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DIFFERENTIATION OF HEMOPHILIA INTO TWO GROUPS*

A Study of Thirty-Three Cases

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PREVIOUS articles[1, 2] have described a new test for the specific determination of antihemophilic factor that measures its effect on the recalcification time of a standard reagent plasma, prepared from the plasma of a typical patient with hemophilia and supplemented with heated platelet extracts. To evaluate the specificity of the new test we re-examined the bleeders previously considered to be hemophiliac by our laboratory. In each case the diagnosis had been based on the following data: the patient's past hemorrhagic history, with or without typical familial transmission and such laboratory findings as prolonged clotting time, poor prothrombin consumption and correction of the clotting defect by a small amount of normal plasma.

We first studied a series of 19 cases of assumed hemophilia. To our surprise, the plasma of 1 patient reacted similarly to that of a normal person in our test system and was able to correct the clotting defect of the other hemophiliac patients. The 18 patients giving similar results with our standard reagent were arbitrarily classified as hemophiliac A, and the other 1 as hemophiliac B. From the plasma of the latter we prepared a hemophilic reagent B (HR-B) by the same procedure used for the preparation of the standard hemophilic reagent A (HR-A).

This article presents a study of 33 cases of hemophilia with these new reagents. All the cases had previously been considered to be of one classic type (3 patients now have or have had a circulating anticoagulant).

METHODS

Test for Antihemophilic Factors

Preparation of HR-A. The blood from a patient with classic hemophilia is collected with dry sodium oxalate (final concentration 1.5 per 1000) in a chilled siliconed container. The blood is first centrifuged at 2000 RPM (revolutions per minute) for twenty minutes. The supernatant plasma is decanted and centrifuged at 4000 RPM for an hour at 1°C. in the international angle centrifuge and then kept for twenty-four hours at 1°C. in the same container. The next day, the tube is centrifuged again twice at 4000 RPM for an hour at 1°C. Though having a normal Quick prothrombin time, this plasma is incoagulable upon addition of an optimal amount of calcium chloride.

Preparation of HR-B. This reagent is prepared in the same manner, but from the blood of a hemophiliac B (Case 16).

Preparation of platelet factor (PF). Citrated human blood (final concentration of sodium citrate 3.8 per 1000) is centrifuged at 1800 RPM for five minutes. The turbid plasma is decanted and re-centrifuged at 800 RPM for five minutes to separate the residual red and white cells. The supernatant platelet-rich plasma is centrifuged at 4000 RPM for an hour at 1°C. in the international angle centrifuge. The sediment of platelets is suspended in a volume of distilled water equivalent to the original plasma and heated at 64°C. for thirty minutes. It is shaken vigorously for fifteen minutes, frozen and thawed twice to ensure a more homogeneous suspension. The final suspension is centrifuged at 2000 RPM for five minutes to remove the insoluble material; the supernatant liquid constitutes the platelet factor.

The reagents A and B as well as the PF are kept at −20°C. without any important modification of activity for several months.

Technic of test. The plasma to be treated is diluted to 1:20 with a buffer of veronal acetate and hydrochloric acid (Michaelis) at pH 7.35. The normal plasma is diluted in the same manner. Four reactions are carried simultaneously. The following results, for example, are the clotting times obtained in that system with a hemophiliac A:

0.1 cc. HR-A + 0.2 cc. saline + 0.1 cc. CaCl2 (0.025 M) . . . ∞
0.1 cc. HR-A + 0.1 cc. PF + 0.1 cc. saline + 0.1 cc. CaCl2 . . . 11 min.
0.1 cc. HR-A + 0.1 cc. PF + 0.1 cc. normal§ + 0.1 cc. CaCl2 . . . 4 min. plasma 1:20
0.1 cc. HR-A + 0.1 cc. PF + 0.1 cc. hemoph. + 0.1 cc. CaCl2 . . . 10 min. plasma A 1:20

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§All normal plasmas used were derived from a pool of at least 5 normal subjects.

The same reactions are repeated with the reagent B. Hemophiliac A plasma behaves like normal plasma with the HR-B. Hemophiliac B behaves like normal plasma with the HR-A.

Other Methods

Clotting time. The Lee and White technic was used to determine the clotting time.

Heparin tolerance test in vitro and *prothrombin consumption test.* These two technics are described elsewhere.[3, 4]

Differential tests for proaccelerin, proconvertin and prothrombin. The procedures are also described elsewhere.[5]

Clinical Data

All the 33 patients studied were males with a hemorrhagic history typical of hemophilia. The hemorrhagic diathesis began in infancy and was characterized by a succession of ecchymoses, hematomas, epistaxes, hematuria and intraperitoneal and retroperitoneal hemorrhages. The clinical diagnosis of hemophilia was not questioned. The family history was positive in 18 cases. The usual laboratory tests (Table 1) gave results consistent with what is found in hemophilia: prolonged clotting time; recalcification time of plasma in the presence of 1 unit of heparin per cubic centimeter always greatly prolonged and often incoagulable; and serum prothrombin time at the fourth hour (two-stage method) always very short and in general less than ten seconds — controls more than one hundred and eighty seconds). One patient (Case 30) had a circulating anticoagulant, and 2 others (Cases 31 and 32) had had an anticoagulant some months or years before, but it was no longer present.

When these cases were studied by the new technics it became apparent that they fell into three distinct groups: 28 cases were considered to be hemophiliac A, 4 cases hemophiliac B and 1 case hemophiliac A + B. Since Type B has only recently been described, the clinical histories of 3 hemophiliac B patients are presented in some detail.*

Case 16. LeM., a 16-year-old French boy, had his 1st hemorrhagic difficulty at the age of 7 months; this was characterized by ecchymosis of the left upper quadrant of the abdomen. Since that time, numerous hemorrhagic episodes had occurred spontaneously or after minimal trauma, such as ecchymoses, persistent hemorrhage (2 or 3 days) from minor trauma to the tongue and lips, repeated hemarthroses of elbows and knees since the age of 5 resulting in considerable restriction of joint movement; hematomas, hematuria, epistaxes and intraperitoneal and retroperitoneal hemorrhages. The diagnosis of hemophilia was first made at the age of 18 months on the finding of a prolonged clotting time of 90 minutes. Of all the treatments prescribed, only whole blood or plasma transfusions were effective. There was no history of a hemorrhagic diathesis in the maternal or paternal side of the family: the mother had 7 brothers and 2 sisters all of whose children were normal. However, 1 of the patient's brothers had presented a history of ecchymoses and hematomas induced by minimal trauma. This child had died at the age of 2½ years from encephalitis. He was not examined in this laboratory, but the clotting time at the age of 13 months

Table 1. *Principal Characteristics of 33 Cases of Hemophilia.*

Case No.	Age	Family History	Clotting Time	Heparin Tolerance Test*	Prothrombin Consumption†	Anticoagulant	Nature of Defect in Antihemophilic Factor	
	yr.		min.	min.	sec.		A	B
1	5	+	28	∞	6	−	+	
2	2	−	22	120	5	−	+	
3	1	+	9	37	5.5	−	+	
4	45	+	12	31	9	−	+	
5	10	+	95	∞	5	−	+	
6	9	+	80	∞	5	−	+	−
7	? 7	−	27	32	14	−	+	
8	45	+	65	∞	9.30	−	+	
9	35	+	40	90	10	−	+	
10	7	−	60	∞	7	−	+	
11	10	+	80	∞	6	−	+	
12	11	? −	45	90	8	−	+	
13	16	+	14	31	12	−	+	
14	4	−	15	25	5	−	+	
15	24	+	13	14	9	−	+	−
16	16	+	110	∞	6	−	−	+
17	28	? −	13	∞	8.50	−	+	
18	34	−	9	12.30	12	−	+	
19	4	−	47	∞	6.5	−	+	
20	2	+	36	∞	7	−	+	
21	32	+	14.30	24.30	9	−	+	−
22	39	+	18	26	3.50	−	+	+
23	38	+	60	∞	4	−	+	−
24	6	−	55	∞	10	−	+	−
25	13	+	90	∞	9	−	+	−
26	6	+	90	∞	12	−	+	−
27	32	+	120+	∞	6	−	+	−
28		−		∞			−	+
29	6	+		45	10	−	+	−
30	18	+	270	150	5	+	−	+
31	20	−	95	∞	4.5	+	+	+
32	12	−			5	+	+	−
33	44	+	18	22	6	−	+	−

*1 unit of heparin in normal subject = 12 min.
†Prothrombin consumption in normal subject = over 1 min.

*A fourth hemophiliac B (Case 28) whose plasma was sent to us from Drs. Jean Bernard and Jean-Louis Beaumont, is not discussed here. This case will be reported elsewhere.

was reported to be 90 minutes. The laboratory tests in the case under discussion were those of a patient with typical hemophilia (Table 2), but the patient's plasma and that of a patient with classic hemophilia corrected each other. There was no evidence of a circulating anticoagulant.

Case 30. Gou., a 19-year-old boy with a familial history of hemophilia, first experienced hemorrhagic manifestations at the age of 1 year. Since that time he had suffered from ecchymoses, hematomas, numerous hemarthroses, resulting in permanent deformity of the joints, and hematuria. Bloody spinal fluid was also observed at the age of 5. In 1952, after a series of transfusions, there was evidence of a circulating anticoagulant, which was still present when the patient was last examined (Table 2).

Case 31. Hen., a 21-year-old man, had a history consistent with nonfamilial hemophilia since the age of 2. The hemorrhagic diathesis was characterized by ecchymoses, hemarthroses, dental hemorrhages, epistaxes and hemorrhages of the palate. After several transfusions, a circulating anticoagulant was demonstrable. In 1951 it was noted that the recalcification time of oxalated plasma (Howell time) was partially corrected by the addition of a small amount of plasma from a patient with classic hemophilia. In March, 1953, when the last studies were performed, the circulating anticoagulant had completely disappeared (Table 2). The mixture of an equal amount of the patient's plasma with normal or hemophilic A plasma gave normal recalcification times, and the prothrombin consumption was restored to normal (more than 180 seconds).

Tests for Antihemophilic Factors

Figure 1 presents the comparative effect of normal plasmas and plasmas in the 33 cases reported on the recalcification time of the hemophilic reagents A and B. For simplification, the recalcification times of the hemophilic reagents with the addition of normal plasmas are charted as a straight line, although there were slight variations from day to day and from one normal plasma to another.

Hemophiliac A (Pure A Type)

Table 3 and Figure 1 show that 28 hemophiliac patients did not correct the recalcification time of the HR-A. The existence of a pure A deficiency was confirmed in 11 of the cases by their corrective effect upon HR-B. It should be noted that only 5 patients tested against HR-B gave a recalcification time identical to those of the controls; 4 of them gave a slightly shorter time (from −45 seconds to −1 minute), and 2 a slightly longer time (+45 seconds). However, we do not consider these differences significant.

The other 17 patients were tested against HR-A alone. It is not certain, therefore, that their defect was only in anti-hemophilic factor A.

Hemophiliac B (Pure B Type)

Four cases (16, 28, 30 and 31) failed to correct the recalcification time of HR-B. They were considered to be of pure B type because they corrected the recalcification time of HR-A to the same extent as normal plasma. Case 31 had had a circulating anticoagulant that was no longer demonstrable. Case 30 still presented a circulating anticoagulant. Nevertheless, the anticoagulant did not interfere with the clot-promoting effect of the plasma on HR-A reagent. This suggests that the 1:20 dilution used routinely for this test eliminated the effect of the anticoagulant. The importance of dilution in the test of this type of plasma is also shown in the following data:

Plasma tested against HR-A	1:10 dil.	1:20 dil.	1:50 dil.
Normal plasma	3 min. 30	4 min.	5 min.
Hemophiliac B (+ anticoagulant)	8 min. 15	4 min. 30	5 min. 30

It is obvious that this patient's plasma had less of a corrective effect when diluted 1:10 than when diluted 1:50, which is the inverse of what is observed with a normal plasma. If only 1:10 dilutions were used, the results could be interpreted as due to a defect rather than an anticoagulant. Thus, dilution of 1:20 or above is necessary to eliminate the effect of this anticoagulant.

Hemophiliacs A + B (Mixed AB Type)

Case 22 failed to correct the prolonged recalcification time of both reagents A and B. The tests were performed on three different occasions with the same results. We were never able to demonstrate the presence of a circulating anticoagulant by the classic tests. Such a case raises the possibility of a mixed hemophilia, with a defect in both factors A and B.

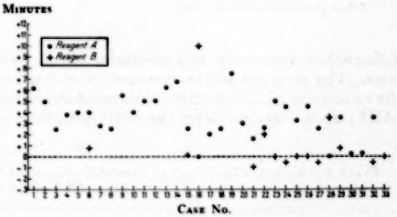

Figure 1. *Clot-Promoting Effect of Plasma from 33 Hemophiliac Patients in Reagents A and B.*

The differences plotted on the ordinate are between the corrective effect of normal plasma and that of each hemophilic plasma upon the recalcification time of reagents A and B. The zero point is taken as the effect of normal plasma simultaneously observed at each experiment. Points plotted on the positive side indicate less corrective ability, and those on the negative side greater corrective ability than the normal.

Comparative Study of Antihemophilic Factors A and B

Tables 3 and 4 present data indicating the concentration of factors A and B in various preparations of plasmas, serums and Armour fibrinogen. Treatment of the test materials delineates the thermolability and absorption characteristics of factors A and B.

In Table 3 the recalcification times of hemophilic plasmas A and B in the presence of an equal amount of undiluted test material are compared with the

control values, in which the test material is replaced by buffer.

Table 4 presents the data on the same test materials determined by the technic for antihemophilic factor previously described.

There are some discrepancies between the results in Tables 3 and 4 that can be explained by the difference in sensitivity and specificity of the two tests. The principle of the two tests is the same: the estimation of the effect of antihemophilic factor (AHF) upon a system devoid of AHF but containing a normal concentration of all other known clotting factors. There are, however, significant differences in the reagents and the technic. The reagent in both tests is a plasma prepared from the same hemophilic blood, but that used in the simple recalcification test contains varying amounts of platelet materials, depending on the amount of centrifugation, and that used in the AHF test is made platelet free and supplemented with a constant amount of heated platelet extract. With any test using such reagents the recalcification time will depend on the concentration of AHF and the presence of an excess of accelerators or inhibitors in the test material. The addition of AHF equivalent to approximately 5 per cent of the normal plasma concentration will correct the recalcification time of both hemophilic plasma reagents (Table 4). It is evident, therefore, that in the simple recalcification time there will be no appreciable difference in the test materials containing more than 5 per cent AHF, whereas in our own method the prior dilution of the test material to 1:20 will disclose variations of concentration between 0 and 100 per cent. Dilution of the test material has the additional advantage of minimizing the effect of any inhibitor or accelerator

TABLE 2. *Results of Laboratory Tests in Cases 16, 30 and 31.*

Case No.	Clotting Time	Recalcification Time	Clot Retraction	Prothrombin Consumption (Serum Prothrombin Time)	Heparin Tolerance Test (Recalcification Time)		Prothrombin Time by Quick Method		Prothrombin, Proconvertin Test	
					Normal Plasma	Patient's Plasma	Normal Plasma	Patient's Plasma	Normal Plasma	Patient's Plasma
	min.	min.		sec.	min.	min.	sec.	sec.	sec.	sec.
16†	90	8	Normal	6	10½	—	14½	16	30	30
31‡	120	13½	Normal	5	8	—	12	12	27	24
30	170	26	Normal	5	8	—	12	15	24	24

*Comparative clotting times induced by addition of minute quantity of bovine thrombin to plasma.
†Average of 4 tests, performed on Sept. 1, 1952, Oct. 1, 1952, and Jan. 7, 1953.
‡Tests performed on March 20, 1953.
§Tests performed on February 12, 1953.
¶Tests performed on March 3, 1953.

TABLE 3. *Recalcification Times* of Hemophilic Plasma in the Presence of an Equal Amount of Test Material (Final Volume 0.4 cc.) in Cases 15, 16 and 31.*

Reagent	Recalcification Time in Case 16		Recalcification Time in Case 31		Recalcification Time in Case 15	
	at 1800 rpm for 5 min.	at 3600 rpm for 15 min.	at 1800 rpm for 5 min.	at 3600 rpm for 15 min.	at 1800 rpm for 5 min.	at 3600 rpm for 15 min.
	min.	min.	min.	min.	min.	min.
Control (buffer at pH 7.35)	12½	19	13½	19½	8¾	9
Normal plasma	3	2½	1¾	3	1¾	2
Normal plasma diluted 1/20	3	2½				
Normal plasma centrifuged at 56°C. for 3 min.		5		12		7½
Normal plasma centrifuged at 56°C. for 5 min.	2½	7		23		8½
Normal plasma centrifuged at 56°C. for 10 min.		9½		26		9½
Normal plasma centrifuged at 64°C. for 3 min.	4½	10¾		22½		9½
Normal plasma centrifuged at 64°C. for 6 min.	12¾	14		25		9¾
Normal plasma centrifuged at 64°C. for 20 min.	15					9¾
Citrated plasma stored at 4°C. for 1 mo.	2					
Stored oxalated plasma	3½		3		6	
Dicumarol plasma (Quick 16 per cent)	2½	2½	2½	4½		1¾
Hemophilic A plasma	3	3½	1¾	3½		
Hemophilic B plasma				30		2½
BaSO4 human plasma	14½			25		2¾
BaSO4 beef plasma	11¾			18		2
Beef plasma (20% asbestos filtered)	2¾	9	3¾	3¾	1¾	1¾
Beef plasma (2 filtrations — 50% asbestos filtered)	7–8			18		1¾
Armour fibrinogen, 1:1000	3¾	14	7¾	16	1¾	4
Human serum stored for 3 hr. at 37°C.				1¾		2
Hemophilic A serum stored for 3 hr. at 37°C.				1		4¾
Human serum stored for 48 hr. at room temp.	1¾	4	2¾	4		5
48-hr.-old human serum heated at 56°C. for 1 min.		8½		7		5¾
48-hr.-old human serum heated at 56°C. for 10 min.		8½		7		5¾
48-hr.-old human serum heated at 64°C. for 3 min.		¾		9½		5¾

*For comparison with control values obtained with buffer at pH 7.

in the test material. For example, bovine fibrinogen or bovine plasma filtered through 20 per cent asbestos pads shortens the recalcification time of hemophilic B plasma whereas the same materials tested on our hemophilic reagent B fail to show any appreciable effect; forty-eight-hour-old human serum corrects the recalcification time of hemophilic A plasma but fails to show any appreciable effect on the HR-A. It is therefore obvious that the corrective effect on the simple recalcification test may be due to nonspecific activities that had little or no effect upon the recalcification time of hemophilic reagents.

From the data in Tables 3 and 4 the following facts can be concluded:

Normal plasma contains antihemophilic factors A and B.

Antihemophilic factor A disappears in oxalated stored plasma, whereas factor B persists.

Plasma from patients treated with Dicumarol contains both AHF A and B.

Hemophilic A and B plasmas correct each other.

Barium sulfate adsorbs factor B, not factor A.

A single filtration through 20 per cent asbestos pads does not remove factor A, but removes almost all factor B. Two filtrations through 50 per cent asbestos pads remove a part of factor A and all factor B.

TABLE 2. (*Concluded*).

Case No.	Proaccelerin Test		Thrombin Time*		Tests for Circulating Anticoagulant Recalcification Time			Antihemophilic Factor A		Antihemophilic Factor B	
	Normal plasma	Patient's plasma	Normal plasma	Patient's plasma	Normal plasma	Patient's plasma	Equal parts normal and patient's plasma	Normal plasma	Patient's plasma	Normal plasma	Patient's plasma
	sec.	sec.	sec.	sec.	min.	min.	min.	min.	min.	min.	min.
16†	20	20	21	21	2	8	2¼	4¼	4	2¼	9
31‡	35	35	23	34	2½	43	9½	3	3	3½	19
					1½	13½	1½				
30	35	30	23	34	1½	10½	9¼	4	4¼	1¼	18

Fresh serum and forty-eight-hour-old serum kept at room temperature are rich in factor B and devoid of factor A.

Both factors are thermolabile.

TABLE 4. *Determination of Antihemophilic Factors A and B.**

Reagent	Recalcification Time	
	Antihemophilic factor A	Antihemophilic factor B
	min.	min.
Control (normal plasma)	2¼	2¼
Control (buffer pH 7.35)	10	9
Normal plasma centrifuged at 56°C. for 3 min.	6	6
Normal plasma centrifuged at 56°C. for 5 min.	8	7
Normal plasma centrifuged at 56°C. for 10 min.	9	9
Normal plasma centrifuged at 64°C. for 3 min.	+12	9¼
Normal plasma centrifuged at 64°C. for 6 min.	+12	9½
Stored oxalated plasma	15	3¼
Dicumarol plasma (Quick 16 per cent prothrombin)	3¼	3¼
Hemophilic A plasma	8½	2¼
Hemophilic B plasma	2¼	8
$BaSO_4$ human plasma	4	9¼
$BASO_4$ beef plasma	4	8½
Beef plasma (20 per cent asbestos filtered)	3¼	8½
Beef plasma (50 per cent asbestos twice filtered)	5½	9
Fibrinogen — Fraction I (Armour)	6¾	12
48-hour-old serum kept at room temperature	11	3

*0.1 cc. of hemophilic reagent + 0.1 cc. of test material diluted 1:20 with buffer + 0.1 cc. of platelet factor + 0.1 cc. of 0.025% $MCaCl_2$.

These findings are in agreement with those reported by Aggeler, White et al.[6, 7]

General Considerations

The 28 cases classified as hemophilia A were all in male patients with clinical histories of classic hemophilia, ranging from mild to severe. Seven patients (Cases 4, 7, 13, 14, 15, 21 and 33) had only minor symptoms, and had clotting times within or slightly above normal limits. When their plasmas

were tested against hemophilic reagent A it was apparent that the concentration of AHF-A was definitely within the hemophilic range.

Eighteen of the 28 patients with hemophilia A had a positive family history.

The 4 cases classified as hemophilia B were all in male patients with symptoms characteristic of severe hemophilia and were clinically indistinguishable from the 21 cases of severe hemophilia A. The usual laboratory clotting studies were similar (bleeding time, clotting time, prothrombin consumption and correction of the clotting time with normal plasma).

Two of the 4 patients with hemophilia B were considered to have a positive family history, for each had a brother with a history of a bleeding tendency, although there was no evidence of a bleeding tendency in the older generations. Several of the patients with hemophilia A were considered to be of the familial type on the same grounds. It is possible that these cases as well as those without any family history were due to a mutation and not to an inherited defect. Biggs et al.[8] present evidence of transmission of Christmas disease (hemophilia B) through clinically healthy females.

It is not yet possible to state precisely the frequency of type A and B in hemophilia. Our patients and those of Biggs and his colleagues[8] total 12 cases of Type B in a group of 83 hemophiliac patients, or 14 per cent.

Among our 28 subjects of Type A, only 1 had a circulating anticoagulant. Two of the four of Type B had or had had a circulating anticoagulant. It is impossible to say whether this apparent greater frequency in the Type B cases is purely coincidental or whether a circulating anticoagulant is more likely to develop.

Discussion

The laboratory and clinical evidence presented above permits correlation of our 4 cases of hemophilia B with 10 similar or identical cases recently described. Aggeler et al.[6, 7] call the new factor, which they recognized while studying a hemorrhagic syndrome in a sixteen-year-old boy previously thought to have a classic case of hemophilia, PTC or "Plasma Thromboplastic Component." Schulman and Smith[9] observed a similar case in a male infant. Biggs and his associates[8] described 7 cases, 4 of them familial. One of these cases, diagnosed by Poole,[10] was reported separately. These authors referred to this newly characterized entity as "Christmas disease," which they differentiated from hemophilia. It should be noted that Pavlovsky[11] and Koller et al.[12] had already pointed out the ability of reciprocal correction of certain hemophilic plasmas.

A review of the data on the previously reported cases indicates the following conclusions: a small number of hemophiliac patients, clinically indistinguishable in all respects, have a defect in plasma factor distinct from the classic antihemophilic factor; and the missing factor seems to be the same in all cases.

The only practical difference between the two forms of hemophilia concerns the treatment. Hemophilia B does not respond to human plasma Fraction I, but treatment with plasma or blood transfusions is effective in both.

The terminology previously proposed (PTC, Christmas factor) does not seem satisfactory, and despite the undesirability of multiple names, it is proposed that the classic antihemophilic factor be called factor A and the new factor antihemophilic factor B. This is not simply a matter of terminology, but an important problem of nosology. The designation PTC could as well be applied to either factor A or factor B. The denomination of "Christmas disease" or "Christmas" factor lacks etiologic and nosologic significance, and furthermore suggests a different meaning.

However, the essential point is that the term "hemophilia" as a syndrome rather than a single pathologic entity seems worth preserving, since hemophilia A cannot be distinguished from hemophilia B by clinical manifestations, familial history and routine laboratory studies. Furthermore, in both conditions, the clotting defect is apparently due to a deficiency in a plasma pro-factor of thromboplastin, distinct from the platelet factors. Classification of the hemophilic syndrome into types A and B has the merit of emphasizing both the clinical similarity and the biologic difference. Since it is now apparent that there are at least two plasma profactors of thromboplastin, it is conceivable that some hemophiliac patients have a deficiency of both factors (as in Case 22). It is also possible that deficiencies in plasma profactors of thromboplastin other than the factors A and B will subsequently be disclosed and then called C, D and so forth. Rosenthal et al.,[13] for instance, report 3 cases of hemorrhagic diathesis under the name of PTA deficiency. For the present, however, these cases must be separated from the hemophilic syndrome, because of their mildness, because of the absence of hematomas and hemarthroses and, above all, because of their occurrence in women. We do not, however, ignore the fact that some cases of hemophilia in women have been reported, but they are exceptional; the concept of a hemorrhagic syndrome occurring almost exclusively in males remains for us a fundamental feature of hemophilia.

Summary

Thirty-three cases of clinically typical hemophilia are reported. From the results of specific determinations of the missing antihemophilic factor underlying the coagulation defect, they could be classified into three groups: hemophilia A (classic hemophilja), 28 cases, hemophilia B (PTC deficiency or Christmas disease), 4 cases, and hemophilia A and B, 1 case.

These three groups exhibit all the classic features of hemophilia in their clinical and genetic history, and in the routine blood-clotting tests. The only difference in the groups was the type of plasma profactor of thromboplastin missing, either factor A or B or both.

Certain important characteristics of these factors are delineated. Factor A and factor B are both present in fresh normal and Dicumarolized plasma, but factor A disappears in oxalated plasma during storage whereas factor B persists. Factor A disappears during coagulation, whereas factor B persists in serum. Factor A is not adsorbed on barium sulfate or asbestos, but factor B is adsorbed in either one. Both factors are thermolabile. Fibrinogen (Fraction I) contains factor A only. Therefore, plasma Fraction I is effective only in the treatment of hemophilia A but not of hemophilia B. However, blood and plasma transfusions are effective in the three types of hemophilia: A, B and AB.

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LENGTH OF LIFE AND CAUSE OF DEATH IN RHEUMATOID ARTHRITIS*

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IT has often been said that the way to live a long life is to acquire rheumatism. The present investigation was designed to test this piece of folklore. More specifically, it is concerned with the shortened life expectancy and major causes of death in patients hospitalized because of rheumatoid arthritis.

The material for this study consists of observations on 583 patients with rheumatoid arthritis[1] who were hospitalized at the Massachusetts General Hospital and were subsequently followed for an average of nine and six-tenths years. It is important to note that, though patients were admitted to this study only as a result of a diagnosis of rheumatoid arthritis established during a hospital admission, a few of them were initially hospitalized for reasons besides the arthritis. Of these 583 patients, 257 were males, and 326 females. During the period of study, 137 died, and for 130 the cause of death is known. Autopsy reports were available in 40 cases. In 90 cases, the cause of death was determined from reports by the attending physicians or from the

TABLE 1. *Deaths and Death Rates per 1000 Patient Years of Observation by Sex and Age Compared to Expected Values Based on Massachusetts Death Rates for White Persons, 1939–1941.*

Life-Table Age*	Male Patients		Female Patients		Expected Value for Male Patients		Expected Value for Female Patients	
	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate
yr.								
<50	33	20.6	20	10.7	7.2	3.9	6.0	2.9
50+	25	38.4	59	39.7	30.6	47.1	61.8	41.6
Over-All.....	58	25.7	79	23.6	37.8	16.4	67.8	20.0

*Life-table age represents the accumulated experience of all the patient years observed in the specified age group.

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death certificates. For the remaining 7 information was insufficient to indicate the cause of death, though the approximate date of death was known.

Short life tables[2, 3] have been constructed according to age at onset, duration of disease on admission to the hospital and sex. The following observations are noteworthy.

TABLE 2. *Death Rates per 1000 Patient Years of Observation, by Sex and Age at Onset, for Patients with Rheumatoid Arthritis.*

Age at Onset	Male Patients		Female Patients	
	Deaths	Death Rate	Deaths	Death Rate
yr.				
<50	49	24.7	36	13.8
50+	9	33.8	43	57.4
Over-All	58	25.7	79	23.6

The over-all mortality rate for the 583 patients was 24.4 per 1000 patients per year, as compared with 18.9 for a comparable age and sex distribution of the population of Massachusetts in 1940.[4] The younger age groups have relatively higher mortality rates in both sexes, whereas those over fifty fare about as well as the general population (Table 1). It also should be noted that the younger male patients fare strikingly worse than the females. This cannot be explained by the age distribution of this group since the females in the group have a higher mean age than the males. One might reasonably ask if this phenomenon is due to a higher mortality among those with spondylitis, which is characteristically a problem of young males. If the males under fifty years of age are divided into those with definite spinal involvement and those with none or only minor cervical involvement, there is no evidence that the mortality rates for the two groups are different. In fact the group with spinal involvement has a slightly but not significantly lower mortality rate.

TABLE 3. *Mortality Rates by Duration of Rheumatoid Arthritis before Admission to the Massachusetts General Hospital.*

Duration of Disease	Patient Years	Deaths	Mortality per 1000 Patient Years
yr.			
1	1214.25	19	15.6
1–4	2200.50	69	31.4
5+	2189.75	49	22.4
Totals	5604.50	137	24.4

Table 2 presents the death rates by sex and age at onset. There is no significant difference between the death rates for males and females for the group as a whole. However, when the question is studied by age of onset there is significantly greater mortality ($P = 0.05$) among men up through the age of forty-nine. At fifty and over, the death rate among women is higher but not significantly so.

Figure 1 demonstrates the difference between the expected number of survivors out of 1000 people in the population of Massachusetts compared with the experience of the 583 patients in this study. There is a notable difference between the curves, for onset before twenty-five years of age and for onset

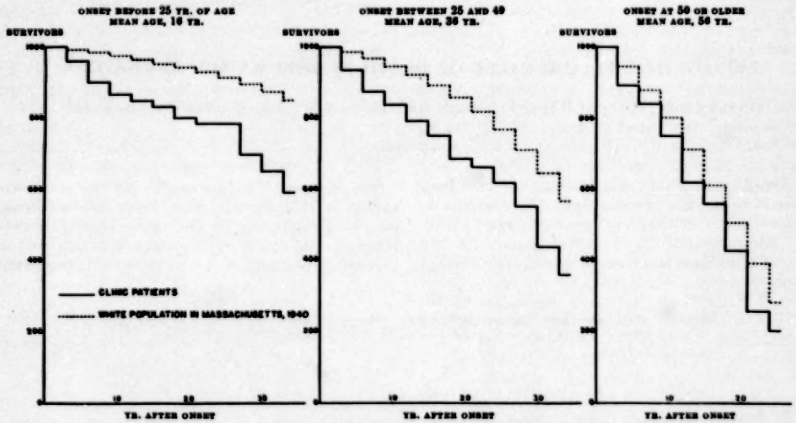

FIGURE 1. *Comparison of Numbers of Survivors among 1000 Patients with Rheumatoid Arthritis with Survivors of 1000 Normal Persons of Equivalent Age by Five-Year Periods and by Age at Onset.*
The Massachusetts population has been adjusted for age by entering the life tables at the average age at onset for each group.

between twenty-five and forty-nine years of age. The difference between the curves when the age at onset is over fifty is not significant.

Table 3 shows that the mortality rates are slightly lower for patients hospitalized during the first year of the disease and after five years of disease and are significantly higher for those hospitalized one to four years after onset of the disease. The phenomenon is not due to any peculiarities of the age distribution of the patients. The group hospitalized one to four years after onset actually has a younger mean age than the other groups. This is further confirmed by an age-specific breakdown of the figures presented.

TABLE 4. *Causes of Death among 130 Cases of Rheumatoid Arthritis.*

CAUSE	No. of Deaths	
Heart disease:		
Myocardial infarction	13	(10.0%)
Valvular heart disease	9	(6.9%)
Hypertensive heart disease	1	(0.8%)
Congestive heart failure and other, unspecified heart disease	9	(6.9%)
Infections:		
Pneumonia	15	(11.5%)
Septicemia	7	(5.4%)
Tuberculosis	6	(4.6%)
Miscellaneous	4	(3.1%)
Nephritis:		
Amyloid	4	(3.1%)
Nephrolithiasis	2	(1.5%)
Pyelonephritis	4	(3.1%)
Glomerulonephritis	5	(3.8%)
Miscellaneous	2	(1.5%)
Cancer	15	(11.5%)
Cerebral accident	12	(9.2%)
Gastrointestinal disease:		
Ulcerative colitis	2	(1.5%)
Perforated peptic ulcer	2	(1.5%)
Miscellaneous	4	(3.1%)
Pulmonary embolism:		
Clot	4	(3.1%)
Fat	0	(—)
Accident	0	(—)
Miscellaneous	10	(7.7%)
Total	130	(99.8%)

Table 5 compares the causes of death in autopsied cases with the experience of four other authors,[6-9] The totals indicate an even higher percentage of deaths from infections but no other striking difference from the preceding tables.

Discussion

The application of life-table methods to this sort of problem is not new. Tuberculosis,[10] cancer[11] and multiple sclerosis[12] have been studied in this manner. The application of the tables to arthritis has substantiated general clinical opinion that rheumatoid arthritis as defined by Bauer[1] tends to shorten life when it is sufficiently severe to warrant hospitalization. But, more interesting than this, the tables show that males who acquire the disease before

TABLE 5. *Causes of Death in Autopsied Cases of Rheumatoid Arthritis.*

CAUSE	ROSENBERG ET AL.[6] NO. OF CASES	YOUNG AND SCHWEDEL[7] NO. OF CASES	BAYLES[8] NO. OF CASES	FINGERMAN AND ANDRUS[9] NO. OF CASES	PRESENT SERIES NO. OF CASES	TOTALS	
Heart disease:							
Myocardial infarction	1	1			5	7	(4%)
Valvular heart disease	7	5			1	13	(7%)
Hypertensive heart disease		2			1	3	(2%)
Congestive heart failure and other nonspecified heart disease	1	4	4	3		12	(6%)
Infection:							
Pneumonia	3	12	2	32	6	55	(26%)
Septicemia			2	9		11	(6%)
Tuberculosis		1	2	7	1	11	(6%)
Miscellaneous	2	1	2			5	(3%)
Nephritis:							
Amyloid	1		2	3	2	8	(4%)
Nephrolithiasis					1	1	(0.5%)
Pyelonephritis	2	1			2	5	(3%)
Glomerulonephritis		2	1			3	(2%)
Miscellaneous		1	1	2		4	(2%)
Cancer	1	3	2	3	5	14	(7%)
Cerebral accident		1	1		2	4	(2%)
Gastrointestinal disease:							
Ulcerative colitis					1	1	(0.5%)
Chronic diarrhea	2					2	(1%)
Perforated peptic ulcer					2	2	(1%)
Miscellaneous		2	2		2	6	(3%)
Pulmonary embolism:							
Clot	3	3			3	9	(5%)
Fat	2		1			3	(2%)
Accident	1					1	(0.5%)
Miscellaneous	4		1		6	11	(6%)
Totals	30	39	23	59	40	191	(99.5%)

Table 5 shows that the mortality rates are slightly lower for patients hospitalized during the first year of the disease and after five years of disease and are significantly higher for those hospitalized one to four years after onset of the disease. The phenomenon is not due to any peculiarities of the age distribution of the patients. The group hospitalized one

The causes of death for the 130 cases in which the cause of death is known are presented in Table 4. It is apparent that 25 per cent of the deaths were caused by infections, 13 per cent by various forms of nephritis, 7 per cent by valvular heart disease, and 3 per cent by pulmonary embolism. All these figures are significantly above the equivalent percentages found in the general population of Massachusetts in 1940.[5] On the other hand, accidents are clearly below the expectation for the population as a whole. Furthermore, hypertensive heart disease and myocardial infarction appear to be below expectation for a group of this age distribution, as is the total of heart disease of all forms.

Table 5 compares the causes of death in autopsied cases with the experience of four other authors,[6-9] The totals indicate an even higher percentage of deaths from infections but no other striking difference from the preceding tables.

Discussion

The application of life-table methods to this sort of problem is not new. Tuberculosis,[10] cancer[11] and multiple sclerosis[12] have been studied in this manner. The application of the tables to arthritis has substantiated general clinical opinion that rheumatoid arthritis as defined by Bauer[1] tends to shorten life

fifty suffer the most marked increase in mortality, possibly because younger men are usually subjected to economic pressures that do not allow them to relax and rest as much as is indicated for persons suffering from this disease. Another partial explanation is undoubtedly related to the clinical observation that rheumatoid heart disease, which can be fatal, is most commonly diagnosed in males under fifty. On the other hand the possibility that spondylitis has a higher rate and hence contributes largely has been ruled out.

In another study it would be most desirable to have more than two age groups and to be able to examine some other factors, such as, perhaps, marital status, as a function of age and sex. The 5600 patient years of observation available for this study have proved insufficient to give significant results for small breakdowns of this nature.

In a study of mortality in Hagerstown, Maryland, Ciocco[13] noted no significant increase in mortality for persons with rheumatism over that in the general population. In connection with this it should be remembered that in his study all forms of rheumatic disorders were included without respect to severity or diagnosis. In this study we have limited ourselves to rheumatoid arthritis of severity sufficient to warrant hospitalization.

It is of interest that accidents, hypertensive heart disease and myocardial infarction seemed less frequent causes of death in the population surveyed than in the general population. Apparently, the diseases of active and hard-driving people have given way to the bronchial pneumonias, pulmonary emboli and urinary calculi of inactive or bed-ridden people. Another point that cannot escape attention is the high percentage of deaths from valvular heart disease. One of these patients had definite rheumatoid heart disease. None of the other cases were autopsied so the exact etiology of the valvular heart disease remains in doubt. It should, of course, be borne in mind that careful study of these patients may have been an important factor in the frequency of the diagnosis of valvular disease. It seems probable, however, that this consideration is more than offset by the fact that the incidence of valvular disease is high in the face of a lowered total incidence of heart disease. The observation that congestive heart failure and unspecified heart diseases constitute a relatively small part of the total heart disease also supports the contention that the incidence — 10 per cent — of deaths from myocardial infarction is low, for there is little chance of an unusual number of missed diagnoses.

The 2 deaths from ulcerative colitis do not form a sufficient numerical bulk to justify comment were it not for the observation of Hench and his collaborators[14] that 4 per cent of their patients with ulcerative colitis also had rheumatoid arthritis.

The observation that infection plays such a large part in causing death among patients with rheumatoid arthritis leads one to hope that the life expectancy of these patients may be materially extended by prompt administration of antibiotic therapy. Furthermore, it suggests that detailed comparison of the mechanisms of immunity of these patients with those of a control series might throw some light on pathogenesis.

Conclusions

Though rheumatoid arthritis is seldom given as a cause of death, the group of hospitalized patients here reported had a higher mortality than would be expected if the group had been drawn from the general population. This was found to be due largely to the fact that younger people, particularly males, succumbed more rapidly than expected whereas the longevity of patients over fifty was not noticeably altered.

The causes of death in rheumatoid arthritis are different from the causes in the population at large. Notable for their frequency as causes of death were valvular heart disease, infections of all sorts, renal disease and pulmonary embolism. Notable for their absence or infrequency were accidental deaths, hypertensive heart disease and myocardial infarction.

These conclusions are sufficiently interesting to warrant further study in larger series of patients, so that the life tables can be broken down into smaller age groups and so that more significant conclusions can be drawn about differences in causes of death between arthritic patients and the general population.

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THE VALUE OF EXFOLIATIVE CYTOLOGY TO THE GENERAL PRACTITIONER*

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MOST practitioners of medicine are, by now, reasonably familiar with the implications of the term "exfoliative cytology" — at least they have heard something about this recently perfected method for detecting and diagnosing cells of malignant tumors in smears of human body fluids. The technic of exfoliative cytology has been greatly improved and, as a consequence, the results of examinations of such smears have become increasingly reliable. It is not at all uncommon for the cytologist to detect the presence of cancer in one or another system of the body before its presence has had time to provoke symptoms that definitely point to neoplastic disease. The practitioner is presumably interested in two questions concerning cytologic diagnosis: whether it is really reliable and trustworthy, and how it can be utilized in his daily practice. The answer to the first is definitely in the affirmative; that to the second immediately poses problems if the physician is practicing in a small community where there are few diagnostic laboratories and fewer cytologic services, or none at all. There are ways of overcoming such difficulties, which are considered below. The first subject discussed is the practical applications of the method in the diagnosis of cancer.

FEMALE GENITAL TRACT

Longest in use, because it was the first to be devised, is the application of exfoliative cytology to the diagnosis of pathologic conditions of the female genital tract. For more than a decade the examination of vaginal, intracervical and intrauterine smears has proved to be soundly reliable and satisfactory. Papanicolaou's work along this line has also introduced several problems that some gynecologists have been quick to deplore on the basis that they have made gynecology more difficult. For instance, the concept of intraepithelial carcinoma (or "carcinoma in situ") has provided material for a great deal of speculation, since it is readily detected in vaginal smears and its presence brings up the question whether or not it represents a genuinely malignant condition. That it probably does in most cases has been indicated by the work of Hertig et al.,[1] Pund and Nieburgs[2] and TeLinde.[3] The fact that a few patients have shown apparent involution or regression of such incipient carcinomas does little to mitigate the fact that many show a progressive development of invasive carcinoma in the course of several years. Should one take advantage of positive diagnosis of incipient carcinoma before it has invaded its local surroundings, or should one wait until it has done so before resorting to surgical measures?

The technic of screening large numbers of cases in a presumably normal population on the chance of detecting undiagnosed carcinoma is another matter entirely. The procedure has definite public-health value, but it is exacting and tedious and possibly turns up fewer cases of malignant tumor than would usually justify the expense of maintaining a cytologic staff for the undertaking. In screening cases in a population of women already showing pathologic symptoms of the genital tract, the matter is quite different, and the method amply justified by results.

RESPIRATORY SYSTEM

The examination of sputum and of bronchial washings has proved to be very reliable; not only can the presence of malignant tumors of the respiratory tract be detected, but also their type may be accurately diagnosed in about 80 per cent of cases.[4] This is because the types of cancer of the lung and its airways are distinctive: two of these, the epidermoid (or squamous-cell) and the anaplastic (or oat-cell) may be accurately diagnosed in almost 90 per cent of the smears. These are probably the commonest varieties of pulmonary cancer, although statistics vary somewhat in different clinics. So characteristic are these growths that cells from their pleural metastases may be correctly diagnosed in about 75 per cent of the smears of pleural exudates that contain them.

STOMACH

The diagnosis of specimens of gastric secretions was, for a long time, about as accurate as the toss of a coin; since Cooper's introduction of the "gastric balloon," however, the picture has completely changed, and the accuracy has risen from about 55 to about 90 per cent. The reason for this pronounced improvement is that the balloon, enshrouded in a hairnet, abrades small bits of tumor-bearing mucosa before the action of the gastric juice and other lytic agents have had a chance to decompose them. When the stomach was simply washed out with Ringer's solution the number of shreds of tissue was small, and that of "stripped nuclei" (or cells denuded of all cytoplasm and hence quite unrecognizable in origin) was correspondingly large. The method is proving to be of great value

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— one that rivals and occasionally surpasses x-ray examination in its accuracy. The reason for this is obvious: in roentgenology one depends on the presence and shape of filling defects as revealed by a change in the normal shadow pictures of the organ. In exfoliative cytology, with the use of the balloon, one can look at the cells of a gastric cancer just as one would in pathological sections. It is a matter of substance as contrasted with shadows.

Colon

A field in which cytology affords excellent results, but in which it is not sufficiently employed, is the colon. To be sure, x-ray films and biopsies are preferred by most physicians, but it should be remembered that x-ray study will reveal cancer only after it has caused sufficient distortion to be detected in the films, and the value of a biopsy is limited by the length of the sigmoidoscope, which scarcely reaches the splenic flexure. What about the cancers of the cecum and the ascending and transverse colon? Intestinal carcinoma is a mucosal, surface growth and probably starts exfoliating its cells into the lumen almost from its origin. The cells may be detected in colonic washings after the tract has been cleansed of feces by catharsis and a short period of fasting. They undergo little deterioration in the secretions of the mucosa and are readily detected in smears of the sediment of colonic washings, where they stand out by reason of the fact that their appearance is usually bizarre and totally dissimilar to that of normal cells.

Urinary Tract

The examination of urinary sediments by cytologic methods is accurate within certain limits. It would equal those of the systems already enumerated except for the fact that tumors of the renal parenchyma, such as renal-cell carcinoma, cannot readily exfoliate cells into the urinary stream. Furthermore, the mucosa of the tract is annoyingly likely to undergo metaplasia as a result of chronic inflammation. If a malignant growth — or a papilloma, for that matter — lies in the mucosa anywhere from the calyxes of the kidney to the external meatus, it exfoliates cells that are readily detectable and diagnosable in smears. The prostate, since it communicates with the posterior urethra, should exfoliate cells from its tumors into the urinary tract, and it does so in many cases. However, even with careful investigation of the urine before and after gentle prostatic massage, and of the prostatic fluid that is exuded, the results have not been as satisfactory as one might theoretically anticipate.

Serous Exudates

It is often necessary to know whether a given exudate or transudate is associated with inflammation or with malignant tumors; one can ascertain this by collecting and centrifugating some of the fluid and then making either smears or "cell blocks" from the sediment. It is well to do both, for one may save time by examining sections made from concentrates of sediment and, at the same time, obtain an increased degree of accuracy by examining whole, unsectioned cells in smears. Naturally, the examination of transudates and exudates, if it reveals cells from malignant tumors, connotes metastasis to a serous membrane like the pleura or peritoneum. If metastasis is already present there can be no question of detecting and arresting incipient carcinoma — the tumor is definitely in its last, inevitably fatal phase. But it often happens that a bloody fluid is aspirated from the thorax or abdomen, and it becomes necessary to determine whether the bloody admixture is attributable to cancer or merely to trauma or inflammation. A negative report in such cases brings relief to practitioner and patient alike.

Breast

Of late some work is being done on mammary secretions, and it has been found that intraductile papillomas and duct-cell carcinomas may be diagnosed on examination of smears of fluid aspirated (rather than expressed) from the nipple. One case in which operation revealed cancer after repeated positive smears and equally positive opinions about the improbability of its presence points a possible moral.

Other Organs

Other applications of the method occasionally show results: there are cases in which cells from carcinomas of the biliary or pancreatic duct are picked up in a Rehfuss bucket on the end of a Levin tube, and carcinomas of the fallopian tubes and of the ovaries have been detected in smears of intrauterine aspirations. It is possible to aspirate directly from the ostia of the tubes, although this is a specialized and ticklish procedure.

The fishmongers' slogan, "If it swims, we have it" could be applied to exfoliative cytology and read, "If it exfoliates, we should find it." This brings up an important consideration — if nothing is found in a smear to justify a diagnosis of malignant tumor, this does not mean that no tumor is present; it simply indicates that no cells have exfoliated, or that if one or two have, they have escaped detection. With methodical examination of the entire smear andt he use of a mechanical stage (which is called "screening") the latter contingency becomes increasingly unlikely. Accordingly, if the practitioner receives a report of Class 1 or Class 2 ("no neoplastic cells noted") it means just that, and he is not justified in telling his patient that no tumor is present; this should be constantly borne in mind.

The examination of spinal fluid and of fluid from the eye is of more than theoretic value; metastatic tumors have been diagnosed in the former, although

primary neurogenous growths have seldom if ever been found. Ophthalmologists are regularly examining smears of ocular fluid in cases of suspected melanoma, with satisfactory results.

One application of the method to dermatologic diagnosis has been very little stressed: the examination of scrapings of dermal lesions, smeared out on microscopical slides and stained by Papanicolaou's method. This obviates the necessity for a biopsy and does not arouse the patient's suspicion and anxiety. Epidermoid (squamous-cell) and hair-matrix (basal-cell) carcinomas can readily be distinguished in this way, and the differentiation of a definitely malignant and a comparatively benign tumor is entirely possible. Contact smears from ulcerating surfaces are also a neglected possibility and have much to offer.

The Practitioner's Responsibilities

The practicing physician can make most of the smears needed for cytologic investigation in his office and then send them in for staining and examination to the nearest cytologist available. Before the making of these smears is discussed, it is advisable to consider briefly the availability of cytologists. In the large cities cytologic laboratories are being rapidly organized. Boston has many of them and has made notable contributions to the discipline.

As a rule it is unfair to expect the local pathologist in a small hospital to perform cytologic investigation in addition to his regular routine. If the hospital is small, the pathologist is probably serving several such institutions, a situation that is particularly common in New York City. In any event, he is far too occupied with clinical and anatomic pathology to be able to spare time for work on smears, since each specimen requires ten minutes or more, even when screened by a technician to exclude non-neoplastic smears. Although any good pathologist can rapidly learn the criteria for making diagnoses on smears, the matter is still tricky, and a few weeks' experience is necessary before he can feel at all secure in his judgment. At any rate, he will need a technician trained in cytology to screen his material; each smear must be scanned from border to border of the coverslip, and all suggestive cells marked with an ink dot so that the cytologist will not waste valuable time in examining a host of non-neoplastic cells. Although the preparation and staining of smears is not at all intricate and can be quickly learned, it takes several months' training for the technician, who is unversed in medical problems, to learn to distinguish the sheep from the goats.

It has become increasingly evident that more pathologists should switch from the usual routines in pathology to the subspecialty of exfoliative cytology. This cannot be done unless the incipient cytologist can command a decent salary and a small, but well furnished laboratory, which since the armamentarium of cytology is very cheap and modest, would require little more than room space. Too great a centralization of diagnostic centers for exfoliative cytology may render the work perfunctory, and it is a job that requires intellectual curiosity and initiative and one in which perfunctory diagnoses are to be deplored.

In preparing smears the practitioner should bear the following directions in mind.

Vaginal Smears

Vaginal smears are easily obtained and made; the vagina that is to be examined should be in a completely resting condition, and smears should never be taken immediately after a digital or instrumental examination, or after physiologic activity. A curved glass tube to which a rubber syringe bulb is attached is introduced into the posterior fornix and a little fluid aspirated and immediately expelled and spread out onto a clean glass slide, which is forthwith immersed in a mixture of equal parts of ether and alcohol (95 per cent). The smear should never be permitted to dry until it has been in the fixative for at least an hour; it may remain there as long as one wishes, without deterioration, if it is inconvenient to remove it at the end of the hour. After it has been fixed, the smear may be allowed to dry and can then be sent to the laboratory, although some cytologists prefer to have the smears submitted in a jar of fixing fluid, or to have them coated with glycerol and covered with another clean slide. Drying before fixation creates distortions of cells and their nuclei that might be mistaken for metaplastic changes.

Because the vaginal fornix constitutes a sort of clearing station where exfoliated cells congregate, one may find vaginal, cervical, endocervical or endometrial cells in the smear, to say nothing of leukocytes, erythrocytes and parasites, such as trichomonas. Occasionally cells from the tubes or ovaries may be found here. Any exfoliating malignant cell may drop into this clearing station and be picked up in the vaginal smear. If the malignant cells are not of obviously vaginal, or epidermoid, origin, the next step is to enter the cervical canal under aseptic precautions with a laryngeal cannula attached to a rubber bulb or Luer-Lok syringe and smears made from fluid aspirated from the cervical canal and the endometrial cavity in succession. The use of a speculum is, of course, necessary in this procedure. Although any nurse or technician can take the material for vaginal smears, the cervical and uterine variety require the services of a licensed physician. Some cytologists recommend scraping visible lesions of the vagina and cervix with a sterile wooden spatula, or a cotton swab, to obtain shreds of tissue as well as discrete cells.

Smears of Sputum

The preparation of smears of sputum is even easier than that of making vaginal smears; the pa-

tient merely coughs deeply and expectorates the product into about 30 cc. of 70 per cent alcohol. Since a shallow cough or perfunctory "ahem" produces nothing but epithelium from the oral cavity, it is imperative that the cough be deep. This may be checked in the office by an unstained smear and a search for pigmented "dust cells" under the microscope. If the cells are present the specimen is valid for examination; if they are not, another trial is indicated. The sputum from the alcohol is spread out uniformly on a slide and further fixed in ether and alcohol. This smear will be of the "clearing-house" variety; to obtain specific indication of which lung may be involved (once malignant cells have been found in the sputum) the services of a radiologist and, possibly, of a bronchoscopist will be needed. If x-ray study is negative the bronchoscopist can obtain washings from the main bronchi after visually examining the tree through his instrument. These washings are kept separate and carefully labeled, since they are usually rather scanty; they may be mixed with equal parts of 95 per cent alcohol, after which they are centrifuged and spread. Usually, they are found to contain fewer and less varied cellular elements than sputum — chiefly ciliated and mucous cells and leukocytes.

Gastric Smears

To be of any great value, these require the use of the gastric balloon; the patient, after a short fasting period, swallows a sausage-shaped balloon made of thin rubber and covered with an ordinary hair net. This is attached to a double tube, one lumen of which is for introducing and aspirating washing fluid, and the other for inflating the balloon after it has been swallowed. The patient passes this apparatus by swallowing a glassful of Ringer's solution to wash it down. The pharynx may be slightly anesthetized in nervous and apprehensive patients. Once the tube is down, all the contents of the stomach are aspirated through the tube, and the organ is thoroughly washed out. The balloon is then inflated and allowed to be drawn to the pylorus, where it is briefly deflated so that it can enter the antrum. Its position in the stomach is determined by gauge rings on the tube. The balloon is reinflated and gently drawn toward the cardia; the process is repeated five or six times in the course of fifteen to thirty minutes, during which the gastric contents are frequently aspirated and collected for centrifugation and smearing. The balloon is then deflated and withdrawn, and its surface inspected for any shreds of tissue (which are removed with a spider forceps and immediately fixed in alcohol and ether). It is then rinsed off into a container with Ringer's solution, and the washings either pooled with the gastric aspirations or kept separate. One then has abraded shreds, gastric washings and rinsings of the balloon's surface. This technic has been described at some length since it is essential for good diagnostic results. Centrifugates are mixed with alcohol and smeared as usual.

Colonic Smears

The patient is given a brisk catharsis the night before the irrigation and fasts until it is over. On the following morning a high colonic irrigation is administered and about 100 cc. of the return is centrifugated, the sediment mixed with alcohol, and smears prepared as usual. This simple procedure should be used more frequently in cases of suspected cancer of the colon.

Smears of Urinary Sediments, Prostatic Secretion and So Forth

Because such smears depend on a tricky technic, it is best to send the urine directly to the laboratory after mixture with equal parts of 95 per cent alcohol. Urine from women should always be obtained by catheterization to avoid contamination by vaginal cells. The specimens are centrifugated, and the sediment spread on prepared slides, with an adhesive coating of egg albumin and glycerol and stained. It has been found wise to cover the smears with thin celloidin as soon as they have been made, which prevents detachment of the cells that have no admixture of mucus to keep them on the glass.

Prostatic Smears

It is recommended that at least three types of sample be taken when the prostate is being investigated: a small quantity of urine voided in a short burst just before prostatic massage; the prostatic fluid that exudes from the meatus during the massage, which should be very gentle; and the rest of the urine in the bladder after the massage has been completed. To "make assurance doubly sure" it is wise to obtain an ejaculate, since this process expels so much prostatic secretion that it would tend to carry malignant cells along with it. Prostatic fluid and ejaculate are smeared directly; the urine is handled as described above.

Breast Smears

Fluid from the nipple should be obtained with a breast-pump and not squeezed out; this avoids chances for metastasis. The fluid is smeared directly, like sputum or vaginal secretion.

Smears of Serous Exudates and Transudates

These are sent in as quickly and in as fresh a condition as possible and mixed with 50 per cent alcohol. The samples are centrifuged, and the sediment smeared in the usual manner. If a "cell block" is desired the sediment is fixed in the tube with any fixing solution desired, and the resulting "button" carefully detached and treated like a piece of tissue, being imbedded and sectioned in paraffin. The stained sections present a solid mass of cells, so that examination is much simpler and corre-

spondingly quicker. Papanicolaou believes, however, that entire cells are preferable to sections of them and therefore relies entirely on smears.

Smears of Skin, Lymph Nodes and So Forth

Lesions of the surface of the skin are simply scraped with a scalpel and the scrapings smeared onto slides coated with glycerol and egg albumin by grinding two slides together over them. Such a smear is often of great diagnostic value and saves taking a biopsy. Excellent smears of lymphoid tissue may be prepared if one rubs the transected surface of a lymph node over a glass slide and fixes it in ether and alcohol.

Other Smears

For smears of spinal fluids, ocular fluids and the like the physician may be left to his own judgment. Spinal fluids require long centrifugation; one may obtain ocular fluids by aspiration or by having the patient open the eye at operation.

Conclusion

It is apparent that there is nothing very formidable in the utilization of exfoliative cytology; there is little or nothing that the physician cannot do himself in the way of obtaining specimens. If there is a trick in this trade, it is the diagnosis, which should admittedly be left to the cytologist. The method has long since passed its experimental stages and is now a practical procedure on a sound basis.

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MEDICAL PROGRESS

MYCOLOGY (Concluded)

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Intermediate Mycoses

Sporotrichosis

It is essential to be constantly alert to diagnose diseases that have a specific form of therapy. Sporotrichosis is such a disease. It responds dramatically, with the rarest of exceptions, to internal iodides. This is doubly important because sporotrichosis has appeared in epidemic form during the last decade, over 2000 cases appearing in a group of mine workers in Africa.[127]

The lymphangitic form[128] is well known, but of recent years much stress has been placed on the atypical, aberrant types of the disease.[129-134] Sporotrichosis may simulate a chronic wart,[127, 131, 134] a furuncle[127-130] or epithelioma.[127, 130] It may produce disseminated subcutaneous nodules,[135] ulcers and even widespread visceral involvement.[132]

Treatment. Well over 2000 cases were treated in the epidemic occurring in the gold mines of Africa. Iodides were a specific cure for the disease in all cases. If a patient is intolerant to iodides, stilbamidine may be worthy of trial.[71]

Moniliasis

Numerous articles attest to the fact that the antibiotics — penicillin, chlortetracycline, oxytetracycline and chloramphenicol — have increased the incidence of moniliasis, especially of the oropharynx and vulvoanal areas.[135-138] It is stated that these drugs may also precipitate pulmonary moniliasis[136] and monilial endocarditis,[139, 140] with its high mortality. Since the antibiotics do not stimulate the growth of *Candida albicans* in vitro (unless the filler contains phosphate ions[141]), most investigators postulate that the endogenous *C. albicans* is released to grow excessively by the destruction of the inhibitory bacterial flora.

Superficial Mycoses

Tinea Capitis

About 1943 an epidemic of scalp ringworm appeared in New York City. It was produced by the anthropophilic fungus, *Microsporum audouini*. Since that time, this disease has disrupted towns and cities in this country, Canada and abroad. It can affect up to 12 per cent of the population under the age of seventeen[142] and persists for months or years. A multitude of medicaments to combat the infection rapidly appeared. The fungicides were supported by glowing clinical reports of cure, but controls based on the pathogenesis of this disease were lacking. In vitro tests using primary isolates, subcultures and stock cultures were relied upon instead of studies of the effect of fungicides on the infected hairs. In 1948 Robinson[142] conclusively demonstrated that numerous popular fungicides, when applied to infected hairs for five days, did not

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prevent the growth of the fungus if the fungicides were completely removed from the hairs before culturing. This has been verified by Kligman and Anderson,[144] who kept hairs immersed in some of these fungicides for over a month.

Outstanding investigative work has been done and is being carried on by Kligman[145] to understand the pathogenesis of tinea capitis. By experimental human infections, he has shown the following: minor trauma is necessary to initiate the infection; only 60 per cent of children are susceptible to infection; the incubation period is three or four days by histologic evidence, but fluorescence does not appear for two weeks and, certainly, without Wood-light examination, no clinical evidence of infection is noted for at least three weeks; there are two types of infection — ringworm of the scalp and ringworm of the hair; active infection takes place in the keratogenous zone just above the bulb and extends downward as the infected hairs grow outward; one can determine activity by epilating peripheral hair and finding fluorescence at the base of hairs (positive fluorescent test), or by finding positive potassium hydroxide preparations from skin scales at the periphery; and there is no further spread of the disease three months after onset of infection, and at this time it is extremely difficult to reinfect experimentally, immunity having been established.

If inflammation is present, there is spontaneous cure without treatment.[144, 146] The incidence of inflammation varies with the different epidemics, but may be as high as 40 per cent.[144]

The time required to cure patients with more than a quarter of the scalp infected is usually three or four times longer than the average.[144]

All these factors must be taken into consideration when fungicides are evaluated in the treatment of tinea capitis.

Rothman et al.[147] attempted to explain spontaneous cure at puberty on the basis of increased production of odd-numbered fatty acids by the sebaceous glands at puberty. These acids were much more fungicidal for *M. audouini* than for *M. canis*. (The popular fatty acids used today in the treatment of tinea pedis are of the same chemical composition.) This theory is not in accordance with some of the basic findings of Kligman[145] in the pathogenesis of tinea capitis and has not been verified. Also, *M. audouini* infection does not disappear abruptly at puberty, and some cases are observed many years after puberty.[149]

Just as hope of definitive treatment for this type of scalp ringworm is in sight, a new epidemic, —more recalcitrant and producing scars and alopecia, —involving adults as well as children, is beginning to appear in the southern half of the United States from coast to coast.[149, 150] This is caused by the nonfluorescent fungus, *T. tonsurans*.

Treatment. X-ray epilation is still the treatment of choice in this disease.[151] It should be used only in properly selected cases on the basis of the criteria outlined above, and should not be given until the infection has been present for three months or more. After this period, reinfection is rare.[145]

Tinea Corporis

For the many doctors who have farmers and their families as patients, ringworm acquired from cattle and horses ("barn itch") is a common skin disease. Four clinical types are found[152-154]: typical ringworm patches, but with less tendency to central clearing; sharply demarcated, erythematous, edematous plaques containing grouped follicular pustules (agminate folliculitis); large, elevated, boggy masses covered with crusts and displaying multiple areas of draining purulent material (kerion); and nodules with a normal overlying epidermis, characterized by marked chronicity (granuloma of Majocchi).

Trauma is the usual precipitating factor.[154] Because of the marked local allergic response, the disease is usually self-limited in four to eight weeks. However, in resistant cases, potassium iodide taken internally is of great value.[152, 154]

T. rubrum, producing another type of ringworm of the body, has been shown to invade subcutaneous tissue in human beings, and therefore is not strictly a superficial mycotic infection. Wilson[155] has reported deep nodular lesions of the legs caused by this fungus. Examination of tissue sections stained by hematoxylin and eosin revealed a granulomatous process extending deeply into the cutis. No fungi could be found. When sections were stained with the Hotchkiss–McManus method, round fungous spores were easily located, and cultures were positive for *T. rubrum*. For the first time, Sternberg et al.[156] were able to produce lesions experimentally in the internal organs of animals with *T. rubrum*. In a study of mice inoculated with this organism, a pathologic process was observed in the omentum, liver, spleen and muscles, culminating in chronic granulomatous lesions simulating those of Hodgkin's disease. It is important to stress that fungi were present in large numbers with the Hotchkiss–McManus stain but were entirely absent with routine hematoxylin and eosin stain. As suggested by Lewis, Hopper and Scott,[157] Sternberg and his collaborators[156] believe that some cases of *T. rubrum* should be classified under the intermediate mycoses.

Tinea Pedis

Although mild ringworm of the feet is usually of no consequence per se, its allergic manifestations are protean and include, in addition to skin lesions, lymphangitis, migrating thrombophlebitis and, questionably, thromboangiitis obliterans.[158-160] In these allergic persons, daily antifungal foot care is necessary to prevent recurrences. This cannot be accomplished unless the commonly associated superficial onychomycosis is eradicated by daily use of a nail brush and the occasional application of the mild

tincture of iodine *U.S.P.*[168] If there is nail involvement, there is invariably concurrent skin involvement.[104]

In addition, constant good foot hygiene is necessary to prevent the occurrence of some types of penicillin reactions, since the dermatophytes have been shown to have an antigen in common with penicillin[165] and the dermatophytes elaborate a substance identical with penicillin in the process of their metabolism.[166] Therefore, tinea pedis may so sensitize a person that the subsequent use of penicillin is complicated by a dermatitis, which, in turn, may be perpetuated by the focus of fungous infection.

Of far more serious consequence is the fact that penicillin can cause death, over a dozen fatal reactions being known to have occurred immediately after the injection of the antibiotic.[167] Penicillin can simulate the various reactions caused by horse serum. Anaphylactic death may occur when horse-serum protein is given to a person with a history of asthma from horse dander. Similarly, before penicillin is given, it is important to know whether the patient has a history of atopy, and particularly whether it is due to the air molds. It is realized that there is no proof as yet of the direct relation between mold allergy and penicillin anaphylaxis, but until this point is clarified, it is advisable to inquire into this possibility.

The anamnesis pertaining to atopy from inhalant molds can be summarized as follows[169]: aggravation of atopic symptoms from the time the ground thaws out until it is covered with snow; persistence of symptoms during the "free period" (end of July) between grass and ragweed seasons; exacerbation when the patient is in the country or near musty basements, woodsheds and so forth; and intolerance to yeast and yeast-containing foods, especially beer.

LABORATORY MYCOLOGY

To establish the definitive laboratory diagnosis, the mycologist must know what mycotic disease or diseases are being considered in the differential diagnosis of any given patient, and must then collect the correct specimens for each specific disease, as described recently by Ajello.[169]

The next step in diagnosis is the direct examination of the various specimens. The Arsac modification of the Hotchkiss–McManus method is an improved technic for diagnosis of ringworm infections and moniliasis.[170] For the beginner it is superior to the potassium hydroxide preparations. It is important to stress that *N. asteroides* appears in Ziehl–Neelsen stains of smears made from fresh purulent material as short branching or *single rods that are definitely acid fast*, simulating tubercle bacilli; however, smears made from the primary culture of the clinical material show partially and irregularly acid-fast elements. With continued transfer on artificial mediums, the organisms tend to lose the acid-fast property.[120] Thus, a diagnosis of tuberculosis cannot be based solely on the findings of acid-fast bacilli in direct examination of sputum.

It should be emphasized that concentration procedures commonly used in the isolation of the tubercle bacilli cannot be relied upon for the isolation of fungi from sputum. Ajello[171] experimentally demonstrated the following facts: *C. albicans* will be completely destroyed by concentration with 4 per cent sodium hydroxide, but will survive concentration with 5 per cent sulfuric acid; although *N. asteroides* is occasionally cultured after concentrating sputum with sodium hydroxide,[124] it was cultured experimentally in every case after the use of 10 per cent trisodium phosphate for the concentration of the fungi; *Cryptococcus neoformans* frequently survives concentration with 4 per cent sodium hydroxide, if the ratio of alkali to the sputum is 1:1, but not as high as 2:1; and *B. dermatitidis*, *C. immitis* and *H. capsulatum* are adversely affected by all the concentration methods used.

Cultures

Sulkin[172] recently reported on laboratory-acquired infections, 63 of which were caused by fungi. Although most of these cases were produced by *C. immitis*,[16] there is evidence that laboratory infection with *H. capsulatum* is not rare.[173, 174] With this warning the various mediums used in culturing of fungi, in addition to the well known Sabouraud's and corn-meal agar, are considered.

Littman's Oxgall Agar

It is often necessary to have a medium to restrict the growth of both bacteria and the rapid-growing, nonpathogenic fungi, particularly in cultures of feces or sputum. Such a medium is Littman's Oxgall agar.[175] However, this medium is not satisfactory for the isolation of *H. capsulatum*,[176] and since it contains streptomycin, Nocardia will be destroyed.

Thiamine-Dextrose Agar

This is Sabouraud's medium with the addition of thiamine or a few drops of crude liver extract. It is necessary for the growth of *T. faviforme*, one of the causative organisms of "barn itch."[152] However, a characteristic, lacy vegetative growth can be obtained if this fungus is planted on Sabouraud's medium and cultured at 37°C.[153]

Brain-Heart Infusion Agar

This is a valuable medium for the isolation of *H. capsulatum*, *B. dermatitidis* and *A. israeli*.[169] For the isolation of *H. capsulatum* and *B. dermatitidis*, 20 units of penicillin and 40 units of streptomycin per cubic centimeter are added, and the tubes are cultured at room temperature. With *A. israeli*, the antibiotics cannot be added, for this organism is sensitive to them. On the other hand,

penicillinase is added if the patient has recently received penicillin. The plates are cultured anaerobically with 10 per cent carbon dioxide at 37°C.

Littman et al.[116] state that the traditional and cumbersome technic of deep veal-infusion-agar cultivation for the isolation of pathogenic anaerobic Actinomyces as recommended in many standard textbooks is unnecessary, since the micro-organisms grow readily in surface colonies on suitable agar mediums and may therefore be isolated in the pure form by simple bacteriologic technics.

Erikson[177] and later Thompson[178] showed that there are two distinct species of anaerobic Actinomyces: *A. israeli*, which causes most of the typical infections in man; and *A. bovis*, which is responsible for most cases of lumpy jaw in cattle. *A. israeli* produces rough surface colonies on plates of brain-heart-infusion agar, whereas *A. bovis* colonies are smooth. Furthermore, *A. israeli* grows as discrete, compact colonies in thioglycolate mediums, whereas *A. bovis* grows diffusely.

Histologic Examination

Weed and Dahlin[179] have stressed the common errors that can be made in an attempt to establish an etiologic diagnosis based exclusively on a histologic examination of tissue. Several cases that were initially diagnosed histologically as tuberculosis were later proved by culture to be systemic mycoses. One of the greatest advances made in the diagnosis of mycotic diseases has been the use of the Hotchkiss–McManus stain for the histologic diagnosis of fungous diseases. Kligman et al.[180] pointed out that the periodic acid Schiff stain was excellent for the demonstration of fungi in tissue.

The procedure is based upon the fact that the cell walls of the fungi are composed of a mixture of cellulose and chitin, both of which are absent in animal tissue. The Hotchkiss–McManus technic specifically stains such substances and others in the chemical class of carbohydrates. Periodic acid hydrolysis releases aldehydes, which can then combine with the Schiff reagent and bring about its recolorization in various shades of red and magenta. Thus, fungi causing superficial, intermediate and systemic mycoses stain various shades of red, and the animal tissue remains unstained. Time and time again, this stain has demonstrated fungi in tissue when the routine hematoxylin and eosin method has failed completely to reveal their presence.

This method of staining should also be of value in distinguishing the extracellular microforms of *B. dermatitidis*, which could easily be confused with *H. capsulatum*.[73, 181]

Animal Pathogenicity

The use of gastric mucin to facilitate systemic fungous infections in laboratory animals has been another noteworthy advance in the field of medical mycology.[182-184] Strauss and Kligman[184] state that the course of experimental infection with various fungi is markedly altered when the organisms are suspended in mucin. Death may be produced with fungi that are otherwise not lethal. The mouse becomes suitable as a susceptible host for all the deep mycoses. Larger and more expensive animals such as the rabbit or less common animals such as the hamster[185] are not necessary.

Gastric mucin did not have a similar effect when the suspensions of fungi were placed on the chorioallantoic membrane of the chick embryo.[184] However, the yolk sac of embryonated eggs has proved to be eminently suitable for the propagation of Actinomyces, Nocardia, *H. capsulatum*, *S. schenckii*, *C. neoformans* and *C. immitis*.[186-188]

Immunologic Procedures

The use of skin tests and complement-fixation and precipitin reactions in the diagnosis and prognosis of mycotic diseases has been thoroughly reviewed by Kligman and DeLamater.[189] Trichophytin, blastomycin, histoplasmin, coccidioidin and sporotrichin are the antigens necessary to perform the required skin testings. It is essential to read these tests at fifteen minutes, twenty-four to forty-eight hours and one week.[2, 190]

Through the use of immunologic procedures the diagnosis, prognosis and duration of coccidioidomycosis can be determined.[2] As mentioned above, a negative skin test with a rising complement-fixation titer signifies a poor prognosis. The precipitin reaction is positive in early cases, but the complement-fixation test must be relied upon for the diagnosis of long-standing cases.

In a report on 40 cases of blastomycosis, Smith[191] divided the cases into four immunologic groups:

Group 1. Positive skin test and negative complement-fixation test. The best prognosis is found in this group.

Group 2. Positive skin test and positive complement-fixation test. The disease is more extensive than in those in Group 1, and the prognosis is poorer.

Group 3. Negative skin test and positive complement-fixation test. This signifies a poor prognosis.

Group 4. Negative skin test and negative complement-fixation test. The disease is too early, or, rarely, there is inability to react because tissue is "flooded with antigen."

The definite prognostic significance attributed to serologic tests in coccidioidomycosis and blastomycosis is controversial when applied to histoplasmosis.[174, 191] Salvin[192] first reported on the use of complement fixation in experimentally infected animals and in 2 human beings in 1947. The first extensive use of the complement-fixation test in human subjects by Furcolow et al.[193] employed a technic devised by Tenenberg and Howell[194] con-

sisting of an adaptation of the complement-fixation test with histoplasmin as antigen. Grayston[174] recently presented an excellent review on the subject of the complement-fixation reactions in histoplasmosis. He concluded that it is of definite value in diagnostic studies for histoplasmosis.

The fact that there are cross reactions, both in skin testing and in complement-fixation tests, among histoplasmin, blastomycin and coccidioidin and other fungous antigens does not invalidate the use of immunologic procedures. By serial dilutions of the antigens used in skin testing and of serum used in complement-fixation tests, the homologous antigen will be detected, for the reaction is more intense and appears at higher dilutions with the homologous antigen or antibody than with heterologous ones.[174, 189]

It is extremely difficult to establish a diagnosis of systemic moniliasis, since the causative organism, *C. albicans*, is endogenous. Agglutinins are found in the serums of normal persons, but titers are low. Children do not exceed 1:10, and adults rarely exceed 1:80. Kligman and DeLamater[189] have observed 2 cases of meningoencephalitis in children that were due to *C. albicans*. In 1 the agglutination titer was 1:320, and in the other it was 1:640. In an adult with extensive pulmonary disease, the titer was repeatedly 1:32,000. Such high titers may prove to be of the utmost diagnostic significance in systemic moniliasis.

Miscellaneous Considerations

Alkiewicz[195] has called attention to a delicate white net, arranged parallel with the transverse axis of the nail. This is visible through a magnifying lens after the application of a drop of cedar oil. Its presence is pathognomonic of onychomycosis.

Sagher[196] noted by histopathologic studies that *T. violaceum* superficially involved the nail plate, whereas *T. rubrum* was more invasive, and that nonpathogenic fungi may become pathogenic to nails.

Haserick[197] may have made an epochal observation. The lupus-erythematosus phenomenon is a specific test and has amplified the understanding of this disease. Haserick noted and proved that fungi such as Aspergillus and *T. mentagrophytes* induced the lupus-erythematosus phenomenon when inoculated into normal serum.

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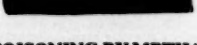
MEDICAL INTELLIGENCE



SUICIDAL POISONING BY METHAPYRILENE HYDROCHLORIDE WITH DOCUMENTATION BY PAPER CHROMATOGRAPHY*

ARTHUR E. O'DEA, M.D.,† AND MAURICE LISS, A.B.‡

BOSTON

METHAPYRILENE hydrochloride is marketed both as an antihistaminic and as a soporific drug under various trade names.[1] As a soporific it can be purchased in any quantity without a prescription.

Reports of its toxicity have been based chiefly on animal experiments.[2, 3]

Wyngaarden and Seevers[4] reviewed the literature on the toxicity of antihistaminic drugs in human beings. They recorded 11 fatal cases, 8 being in children under two years of age. Of the 3 deaths in adults, 1 was a suicide with Benadryl.[5] Only 1 of the 11 cases was poisoning with methapyrilene hydrochloride.[6]

No toxicologic data on blood or gastric contents were reported in any of the fatal cases. The authors concluded that infants and children seemed predisposed to convulsions, whereas adults tended to manifest central-nervous-system depression.

CASE REPORT

The following case§ was studied pathologically and toxicologically by our laboratories.

The decedent, a 19-year-old single woman, was found on the floor of her bedroom in convulsions. A scream had summoned her neighbors. At her side were 2 empty bottles labeled methapyrilene hydrochloride (Dormin). A physician sent her to a hospital, where she was found to be cyanotic, continued to have convulsions and died 45 minutes after admission, 1½ hours after she was first found.

Autopsy showed the body of a well developed, well nourished woman of about the stated age. A frothy, blood-tinged fluid oozed from the mouth.

The heart, spleen, liver, endocrine system and kidneys were normal. The lungs were edematous and congested, each weighing 500 gm. The bronchi were lined by a fiery-red mucosa, suggesting aspiration of gastric content, and there was fresh lobular hemorrhage.

The stomach contained approximately 300 cc. of pink, thick, mucoid material. The mucosa showed no injection or ulceration and was coated with tenacious pink mucus. No fragments of the capsules were found, but the pink color of the mucus was similar to that of Dormin capsules.

The urinary bladder was empty. The uterus was lined by menstrual endometrium. The cervix was eroded.

There were petechial hemorrhages on the undersurface of the scalp. The brain, which weighed 1350 gm., was swollen and firm.

A Model DU Beckman quartz spectrophotometer, with 1-cm. quartz cells, was used to obtain all spectral data in this paper. A 25-mg. capsule of methapyrilene hydrochloride was diluted to a concentration of 10 gamma per cubic centimeter and examined in the spectrophotometer. A spectrum characteristic of methapyrilene hydrochloride previously recorded in these laboratories was obtained on this capsule (Fig. 1).

One gram of stomach content was made alkaline with 10 per cent sodium hydroxide and extracted with 3 10-cc. portions of chloroform. The chloroform was extracted with dilute hydrochloric acid, and the aqueous portion examined in the spectrophotometer. A spectrum of methapyrilene hydrochloride was

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obtained (Fig. 2). The stomach was calculated to contain 240 mg. of methapyrilene hydrochloride per 100 gm. of original stomach content. Total stomach contents comprised 720 mg. of methapyrilene hydrochloride.

Five cubic centimeters of blood serum was made alkaline with 10 per cent sodium hydroxide and extracted with 2 20-cc. portions of chloroform. The chloroform was evaporated to an approximate volume of 1 cc., and an ascending paper chromatogram was made with this extract.[7] By the same procedure a paper chromatogram was made with methapyrilene hydrochloride.

The solvent system for the paper chromatograms was n-butanol and glacial acetic acid in a 10:1 ratio, saturated with water.

The chromatogram was allowed to remain in the solvent system for 16 hours. It was then removed and dried. The methapyrilene hydrochloride chromatogram developed a spot at Rf 0.66 on treatment with Dragendorff's reagent.[7] The chromatogram obtained from the decedent's blood serum was cut approximately in half vertically. One portion of the chromatogram developed a spot at Rf 0.66 on treatment with Dragendorff's reagent. The area corresponding to Rf 0.66 was cut out of the other portion and eluted with dilute hydrochloric acid. The solution was examined in the spectrophotometer, and a spectrum characteristic of methapyrilene hydrochloride was obtained. The serum was calculated to contain 1.2 mg. of methapyrilene hydrochloride per 100 cc.

Known amounts of methapyrilene hydrochloride were added to serum. Chromatograms were prepared as described above. Recovery of the drug averaged 89 per cent.

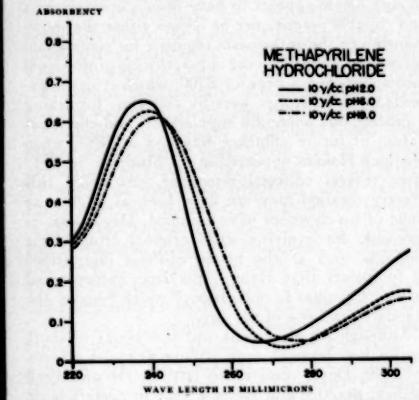

FIGURE 1. *Absorption Spectrums of Methapyrilene Hydrochloride.*

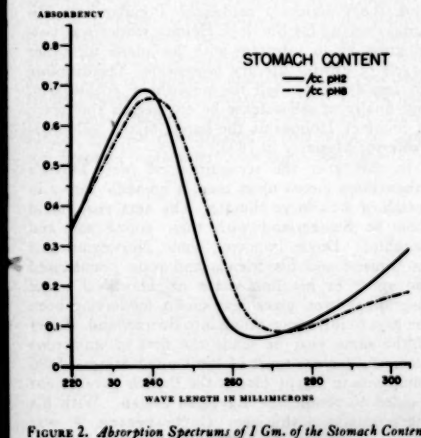

FIGURE 2. *Absorption Spectrums of 1 Gm. of the Stomach Contents after Acid Extraction.*

DISCUSSION

The autopsy findings were consistent with convulsions and anoxia. No cause of death was apparent morphologically. Chemical analysis of the blood and stomach contents accounted for approximately 747 mg. of methapyrilene hydrochloride, which is equivalent to 29 25-mg. capsules of Dormin. It is not known whether a physiologically active metabolite of methapyrilene not measured in our chromatograms exists.

Because of the amount of the drug ingested and because a history of a recent disappointment was obtained, the death was ruled a suicide.

SUMMARY

A case of suicidal ingestion of at least 747 mg. of methapyrilene hydrochloride is presented. A method for estimating methapyrilene hydrochloride in blood serum by paper chromatography is described.

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DOCTORS AFIELD

Arthur Conan Doyle

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ARTHUR CONAN DOYLE was born in Edinburgh in 1859, the fourth of 10 siblings. His parents were Irish Catholics of distinguished, but by no means affluent, ancestry that was endowed with considerable artistic talent on the paternal

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side. Arthur's formal education was under Jesuit auspices, first at Stonyhurst and then at Feldkirch in western Austria. It was during his year on the Continent that he was first introduced to the mysteries of Edgar Allan Poe, whose C. Auguste Dupin was the forerunner of Sherlock Holmes and of today's fictional analytical detectives.

Doyle's mother seems to have chosen the career of medicine for him, and she bore the brunt of the stress on the family budget imposed by his medical education. He matriculated at the University of Edinburgh in 1876, receiving his medical degree five years later. He appears to have been only an average student despite other evidence of sound intellectual equipment, but he never displayed a burning enthusiasm for medicine as a career. The necessity for earning money during his study of medicine furnished some distraction. So likewise did various extracurricular interests. He was possessed of a large, powerful and well co-ordinated physique and a tremendous vitality that kept him actively interested in all forms of athletics well into middle life.

His years at Edinburgh were significant chiefly in his contact with Joseph Bell, the eminent surgeon at the Royal Infirmary, who was famous for his keen observation and his unusual powers of deduction. Bell loved to astound his students by revealing various minutiae of a patient's daily life that he had deduced from a few minor physical characteristics. On one occasion he was demonstrating a patient with a submaxillary swelling due to the occlusion of the salivary duct by a food particle. The students displayed their customary deferential wonder when the patient confirmed Bell's deduction that he was a musician and played a wind instrument. There was some dismay when it was revealed that the instrument was an accordion, but the idol was restored to his pedestal when the patient admitted that he was a glass blower by trade. There is little doubt that Sherlock Holmes was eventually created in Bell's physical and intellectual image even though Poe's Dupin furnished the original inspiration. Before taking his degree in 1881 Doyle served during a vacation as medical assistant to a practicing physician and during that time sold his first short story, but Sherlock Holmes was not created until 1886. In 1880 Doyle went as ship's surgeon on a seven-month whaling cruise to the Arctic, and shortly after graduation he served in the same capacity on a cruise to the African gold coast.

In 1882 he declared himself an agnostic, forsaking Roman Catholicism and with it the active material support of influential relatives that might have ensured a successful medical practice. His first venture into medical practice was in the role of quasi-partner to a near-quack contemporary in Plymouth. After a few months he set up for himself in Portsmouth and here began his literary career, which was to supplant the practice of medicine eight years later. In 1885 he took his postgraduate doctoral degree at Edinburgh, and a few months later he married Louise Hawkins, whose brother he had cared for in his fatal illness. Although Doyle appears to have been a conscientious and capable practitioner he lacked either the showmanship or the enthusiasm requisite for commercial success; in that third year of practice his professional income reached a peak of £300, which it never exceeded. Short stories were by this time furnishing a modest but uncertain supplement, and the foundation of future affluence was laid in 1887, when Sherlock Holmes appeared in "A Study in Scarlet" after several editorial rejections. Although this literary creation may not have been as original as some of his devotees have assumed, Doyle was responsible for evolving some original criminologic methods such as the plaster-of-Paris impressions of footprints that Hans Gross later incorporated in his "Criminal Investigation," which became the standard textbook of the day.

Although his six novels and two books of short stories had brought only trifling financial returns by 1890, Doyle resolved to jettison his dwindling medical practice and spend a year in postgraduate medical study on the Continent. On his return he set up in London as an eye specialist but not a single patient ever rang his bell. By this time Sherlock Holmes had made him famous, and after a nearly fatal attack of influenza he definitely forsook the practice of medicine. Popular and editorial demand for Sherlock Holmes stories was now so great as to interfere with his plans for other novels of greater literary pretension. Quadrupling his fees failed to dull the publishers' enthusiasm, and finally in self-defense he engineered the death of Sherlock Holmes at the hands of the villainous Professor Moriarty in 1893.

In this year the recognition of Mrs. Doyle's tuberculosis forced upon them a nomadic career in search of a curative climate. The next year found them in Switzerland with their young son and daughter. Doyle imported some Norwegian skis for himself and his friends and soon popularized the sport in his immediate neighborhood. One biographer even gives him credit for having been the first to introduce skiing into Switzerland. Later in the same year he made the first of numerous successful lecture tours of the United States. 1896 found him in Egypt just as the British government decided to retake the Egyptian Sudan. With his characteristic enthusiasm Doyle became a war correspondent for the *Westminster Gazette*, and, although he had to return to England before hostilities began, the adventure furnished background material for yet another novel.

In response to insistent demands he revived Sherlock Holmes in a play, which, in garbled form, starred William Gillette in 1899, but he did not

resume the writing of Sherlock Holmes stories until 1903. In the meantime the Boer War began to divert his energies from his high-pressure literary production. Here was another worthy cause for him to espouse, and in he leaped. He volunteered as either a combatant or a medical officer and eventually joined the Langman Hospital group in a quasi-medical capacity. After landing in South Africa in 1900 he began to observe at first hand the medical and military blundering that almost lost the war for Britain. He, too, fell a victim to the ubiquitous "enteric [typhoid] fever," but thanks to his rugged constitution and to previous inoculation he survived the ordeal. On his return he wrote his prophetic article on Army reform, which must have pushed the old guard to the verge of apoplexy. The same convictions led him to stand for Parliament from an Edinburgh district; he lost the election by only a small margin. In 1902 he was knighted in recognition of his literary accomplishments as well as for his services to the Crown as a pamphleteer against anti-British atrocity propaganda arising out of the Boer War.

A year after his wife's death in 1906 he married Jean Leckie, and this union was eventually blessed with two sons and a daughter. Now he began to be personally thrust into the role of Sherlock Holmes, first in the redirection of blind justice that had gone astray and later in the solution of unsolved crimes. He seems to have played this role with both vigor and discretion and no small degree of success, thanks to the application of truly Holmesian methods. Unfortunately, he did not always apply the same penetrating analysis to his own affairs, and considerable amounts of his now substantial fortune were frittered away on various harebrained business ventures. Bogus gold mines, sunken Spanish treasure and a coal mine containing fireproof coal were among his less profitable investments. In the meantime numerous plays and a constant stream of novels flowed from his pen, as well as pamphlets protesting the atrocities in the Belgian Congo. One of his most prophetic stories, entitled "Danger," was published in 1912. In it he depicted England brought to terms by a small nation with a few ultramodern submarines and blueprinted with surprising accuracy many of the practices of naval warfare for the next thirty years.

World War I found Doyle in the usual eager civilian's ancillary roles. The Home Guard, trips to the front as a war correspondent, the design of body armor, which failed to impress the War Office, the invention of an inflatable life belt — all came under the spell of his contagious enthusiasm. In 1915 his brother-in-law, Malcolm Leckie, died of wounds, and a coincidental spiritualistic experience finally converted Conan Doyle to a belief in spiritualism, which had first aroused his skeptical interest in 1887 and in which he had dabbled during the intervening years. This was a profound shock to his literary fans, who had always regarded him as the epitome of reason and sound common sense. By 1919 this had become a monomania, and thenceforth he wrote only in this cause. By 1923 he had traveled 50,000 miles, had addressed 250,000 people at home and abroad, and had spent the equivalent of $1,000,000 of his own funds to promote the cause of spiritualism. He died in 1930, about seven months after a premonitory coronary occlusion.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39401

PRESENTATION OF CASE

A thirty-eight-year-old sales clerk was admitted to the hospital because of back pain and cough.

About seven years before admission the patient noted the onset of a dry hacking cough that was often brought on when he lay on his left side and was associated with nonradiating left subscapular pain. These symptoms persisted, and four years before admission, the pain grew worse, and began to extend to the right subscapular region. At this time the patient was admitted to another hospital, where an exploratory operation was performed, after which he was told he had an inoperable blood-vessel tumor. Two years before admission, dysphagia began, and wasting of the muscles of the right hand became apparent. The right subscapular pain was now so severe as to require about 25 aspirins a day. During the past two or three years he had "spells" lasting ten or fifteen minutes during which he was unable to speak. Headaches were frequent. Shortly before admission, swelling of the ankles was noted. His symptoms had become progressively worse. He denied ever having had syphilis.

Physical examination revealed an anxious man in no distress. The chest was deformed, the left side of the sternum projecting anteriorly, and on the left the ribs were depressed to form a shallow hollow in the anterior chest wall. The left radial pulse was strong, but the right could not be felt. A weak brachial pulse was palpable on the right. The right femoral pulse was strong, and the left weak. The right dorsalis-pedis pulse was strong, and the left absent. Both carotid pulses were strong. A tracheal tug was felt, and marked pulsation seen in the right supraclavicular space. The point of maximal impulse of the heart was at the costal margin and to the right of the midclavicular line. A thrill and a forceful systolic beat could be felt over the upper part of the left side of the chest anteriorly, and were associated with a harsh, Grade 4 murmur. Wasting of the right thenar muscles was apparent.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 90 diastolic, in the left arm and 90 systolic, 80 diastolic, in the right.

The urine was normal. Examination of the blood demonstrated a hemoglobin of 13.4 gm. per 100 cc. and a white-cell count of 8500. The total protein was 7.1 gm., with an albumin globulin ratio of 1.7, the nonprotein nitrogen 28 mg., and the fasting blood sugar 88 mg. per 100 cc.; the prothrombin time was 20 seconds (normal, 14 seconds). Serologic tests for syphilis were negative. An electrocardiogram showing low T waves was not quite normal, but was not diagnostic. Roentgenograms and fluoroscopic examination of the chest disclosed paralysis of the left vocal cord and perhaps weakness of the right. A huge aneurysm was seen to involve the arch and proximal descending aorta (Fig. 1, 2 and 3). The aneurysmal sac was partially calcified. The ascending aorta was somewhat dilated, as was, probably, the innominate artery. The esophagus was displaced anteriorly and to the right, and the trachea anteriorly. No bone erosion was apparent. The lungs were emphysematous, with blebs at the right apex and a few flecks of calcification at the left apex. The heart was not grossly enlarged and showed normal pulsations. An intravenous pyelogram was normal.

FIGURE 1.

The patient refused recommended operation and was discharged. Several days later he returned,

having changed his mind. Findings were as before, and on the third hospital day an operation was performed.

Differential Diagnosis

Dr. James H. Currens*: I should like to know what tests for syphilis were done and whether a quantitative serologic test was done.

Dr. Robert R. Linton: We ordered quantitative serologic tests, but the report had not come through.

Figure 2.

I thought it was of academic interest so far as the surgical treatment was concerned.

Dr. Currens: I should be inclined to agree with Dr. Linton that the diagnosis seems quite straightforward in this case and should like to discuss the case as if I really knew the diagnosis. The points in favor of the diagnosis will be discussed as well as the points against it, which are also noteworthy. There seems to have been little doubt in the mind of the radiologist that this patient had an aneurysm. Perhaps I may see the x-ray films first to orient myself about the size and position of the mass in the chest, which was described as being saccular and in approximation to the aorta.

Dr. Joseph Hanelin: There seems to be little question that we are dealing with a huge aneurysm of the thoracic aorta. There is saccular dilatation of the transverse portion and of the proximal descending portion and perhaps a shade of enlargement of the ascending aorta (Fig. 1, 2 and 3). The heart is not particularly enlarged. The esophagus is displaced toward the right and anteriorly, and the trachea is displaced anteriorly. There are some old calcified scars in the apex and base of the left lung, and there appear to be emphysematous blebs at the right apex. The aneurysm probably extends to involve the innominate and subclavian arteries on the right side. On fluoroscopic examination it is possible to see the arytenoids move during phonation, and on this basis the fluoroscopist could observe the effect of pressure on the laryngeal nerve. The

Figure 3.

pyelogram was normal except for duplication of the left renal pelvis.

Dr. Currens: Do you think there are two sacs or one lobulated sac?

Dr. Hanelin: I think the aneurysmal dilatation is continuous. Although originally erosion was not suspected, there is some spreading of the ribs on the left side, and there may be some erosion of the anterior ribs superiorly and possibly also some erosion of the sternum.

Dr. Currens: Do you see any calcification of the ascending aorta? Calcification in the wall of the aorta sometimes helps in the diagnosis of syphilitic aortitis. Is that not true?

Dr. Hanelin: Yes; it is. There is none in the ascending aorta on these films. When calcification primarily involves the ascending portion of the

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aorta or involves the ascending portion to a greater degree than the remainder, we often find that we are dealing with syphilitic aortitis.

DR. CURRENS: Do you see calcification within the mass?

DR. HANELIN: In one of the films some calcification is visible within the wall of the aneurysm, primarily in the transverse portion.

DR. LINTON: Are these the only x-ray films you are going to show?

DR. HANELIN: They are the only ones I intended to show; there was no great revelation from the angiocardiogram.

DR. CURRENS: I should like to ask Dr. Hanelin one more question. Would you expect the patient to have had hoarseness if he had had paralysis of one and weakness of the other vocal cord? If this observation is to be taken at face value, I should expect some hoarseness or a history of hoarseness.

DR. HANELIN: I think there is generally hoarseness with paralysis. Was there hoarseness in this patient, Dr. Linton?

DR. LINTON: I did not notice it in talking with him.

DR. CURRENS: I am told by the otolaryngologists that the hoarseness may disappear after a time even though one vocal cord is weak or paralyzed.

I should like to make a diagnosis of syphilitic aneurysm of the aorta and to give my reasons. Certainly, the history of cough and chest pain is quite consistent with an aneurysm involving the arch and descending portion of the aorta. The duration of seven years is somewhat disquieting. The symptoms are frequently more progressive than this patient demonstrated, but with clotting in the aneurysm it is quite possible for the aneurysm to remain the same size for many years, sometimes for ten or fifteen years. The calcification, although within the sac itself, does not help much because clotted blood occasionally calcifies and is demonstrable on the x-ray films. The involvement of the innominate artery on the right undoubtedly accounts for the reduced circulation of the right arm and hand. The tracheal tug is a classic sign. The cervical pulsation is merely a reflection of expansile pulsation or possibly of transmitted pulsation to the neck, and since this mass was predominantly on the left it is understandable that the pulsation was on the left. The location of this mass is characteristic of syphilitic aneurysm, which involves the arch or descending aorta. The fact that it was saccular is quite consistent. The patient was a male, which is also in favor of syphilitic disease since there is a ratio of males to females with cardiovascular syphilis of about 3 or 4 to 1.

There are two or three disquieting features about this case, however. At the age of thirty-eight years, the patient had symptoms dating back seven years, which means that he had the aneurysm at the age of thirty-one, an unusually young age for a syphilitic aneurysm; the early onset does not exclude the diagnosis, however, since syphilis may reach the tertiary stage in two to five years in an occasional patient. Moreover, I do not know when the primary infection may have occurred. If infection started at the age of fifteen, it is conceivable that it became tertiary at this age. The duration of the chest pain is somewhat against the diagnosis. The negative serologic tests bother me considerably more than they did Dr. Linton. I think it is quite important to obtain a quantitative serologic test in a patient with these findings since by that means only is it possible to pick up the "zoning" phenomenon sometimes referred to as the prozone phenomenon — that is, in the low dilutions of serum, the serologic test is negative; it then becomes positive on dilution and on still further dilution becomes negative again. Even if this quantitative test had been negative, I do not think it would exclude the diagnosis. Dr. Chester Frazier,[1] of this hospital, has reported 9 cases in a series of 164 that were diagnosed as cardiovascular syphilis in the absence of positive quantitative serologic tests. Since this was a clinical study, the results may not agree with the anatomic diagnosis, but at least 9 of 164 cases, about 5 per cent, may have negative quantitative serologic tests with enough other evidence for one to make a clinical diagnosis of cardiovascular syphilis. I do not know of a study correlating negative serologic evidence for syphilis with a positive autopsy diagnosis of cardiovascular syphilis.

Other types of aneurysm should be considered. Congenital aneurysm, sometimes referred to as Marfan's syndrome, which is a congenital anomaly associated with arachnodactyly, highly arched palate and usually dislocation of the lenses of the eyes, is an accepted syndrome originally described by a French pediatrician. Those aneurysms are usually dissecting, not saccular in appearance as this mass was. Dissecting aneurysm of the aorta would be highly unlikely in a patient of this age without hypertension and with symptoms for seven years. The only finding consistent with dissecting aneurysm is the disturbance of circulation to the left leg, which is hard to explain on any other basis with the possible exception of embolism from the heart or from the aneurysm; embolism from an aneurysm is extremely rare. Mycotic aneurysm seems well excluded on the basis of size, duration and lack of fever.

Other conditions that should be considered are extravascular tumors in proximity with the aorta that might produce signs quite in keeping with an aneurysmal dilatation or sac bulging from the aorta. A dermoid cyst, I suppose, should be considered,

but the mass was in an unusual position for a dermoid cyst; the fact that the mass had calcification in it does not help because calcification is occasionally seen inside a dermoid cyst.

The headache is still unexplained. I should like to know whether or not there was central-nervous-system syphilis in a patient who presumably had cardiovascular syphilis. I think cerebrospinal-fluid examination would have been desirable in this case. The "spells" that the patient had I am also unable to explain. Vertigo is a symptom that is described by some patients with aneurysm of the aorta and is unexplained so far as I know.

Clinical Diagnosis

Syphilitic aortic aneurysm.

Dr. James H. Currens' Diagnosis

Syphilitic aortic aneurysm.

Anatomical Diagnosis

Dissecting aneurysm of the aorta, healed.

Pathological Discussion

Dr. Benjamin Castleman: Dr. Linton, would you discuss the preoperative findings?

Dr. Linton: I should like to defend my statement that the serologic test was only of academic interest; I was speaking from the point of view of therapy. Since this man had an aneurysm, although we were interested in the quantitative blood Hinton test, we did not believe that it would make any difference to the therapy whether it was positive or not.

When I saw the patient in 1951, I advised him to have something done, but he refused, probably, in part, because he had had an exploratory operation a year or two previously and the surgeons had merely backed out. The angiocardiogram, I think, is worth showing even though the changes may be difficult to see. Having seen the inside of this man's chest, I know exactly what it shows although I was not so sure before I operated. The arch of the aorta is clearly seen, with the right innominate and the left common carotid arteries coming off it, and appears to be normal. The left subclavian artery cannot be seen.

Dr. Castleman: Will you tell us what you did at operation?

Dr. Linton: I was suspicious that this was not a syphilitic aneurysm when I first saw this patient, but I decided that, despite the negative blood Hinton test, on a percentage basis I had to make a diagnosis of syphilitic aneurysm because 95 to 99 per cent of thoracic aneurysms are syphilitic. Our operation was designed either to remove this aneurysm or to do a plastic procedure upon it. Dr. Michael E. DeBakey, professor of surgery at Baylor University College of Medicine in Houston, Texas, who was here at the time, reported that he had removed a number successfully; for that reason we asked him to help with the operation. The aneurysm was found to arise from the arch of the aorta immediately distal to the left common carotid artery. The aorta proximal to that part was normal in size and appearance so far as I could tell grossly. The aneurysm was excised. The aorta had to be clamped completely off just distal to the left common carotid artery — the left subclavian artery arose from the aneurysmal sac. The clamp was on the arch of the aorta for an hour and a half so it would have been interesting to know what would have happened to the spinal cord if the patient had lived. We had great difficulty in controlling the bleeding after we had re-established circulation by means of end-to-end anastomosis of the descending thoracic aorta with the transverse arch. Blood kept coming from somewhere, but we could not ascertain where; it was not until Dr. Castleman discovered the actual disease that we knew what our difficulty had been. The patient died on the operating table in shock from uncontrolled hemorrhage.

Dr. Castleman: At autopsy the right and left common carotids came off the aorta. There was no innominate artery. The right subclavian artery, which was resected with the operative specimen, was occluded at its origin by old organized thrombus. The left subclavian artery was also tied at operation. The aorta was found to have a healed dissecting aneurysm. The original lumen between the intima and the dissection channel can be seen in the autopsy specimen, but we did not recognize it in examining the operative specimen. We were able to piece the aorta together after autopsy and realized that the smooth-lined hole about 1.5 cm. in diameter that opened into the saccular dilatation of the operated specimen represented an old epithelized tear into the dissection channel. The dissection in turn re-entered the original lumen through the orifice of the right renal artery, which had been torn completely at the time of the original dissection. Blood to the right kidney had subsequently entered the renal artery from the new channel.

We have now had 2 or 3 dissecting aortic aneurysms, and a few have been reported elsewhere, in which the dissection bulged so much that it simulated the ordinary saccular aneurysm and was mistaken for a syphilitic or arteriosclerotic aneurysm. When the surgeons anastomosed the aorta in this patient they apparently did not realize that there was another channel; the bleeding that they could not control was coming from the second lumen. Although they did suture the original aortic lumen

they did not suture the healed dissection channel very tightly.

DR. LINTON: What we did was to anastomose the primary aortic lumens, and we left the healed dissected lumen open because we did not know it was there.

DR. EDWARD F. BLAND: It is interesting that the lower opening saved the patient's life originally and then did him in at operation.

DR. LINTON: I believe that this may have represented an aneurysm that started in the left subclavian artery.

DR. CASTLEMAN: I doubt if that is so because microscopical examination of the entire aorta showed a severe medial necrosis such as is seen in the younger patients with dissecting aortic aneurysm. Gore,[2] who studied the cases at the Armed Forces Institute of Pathology, described more than 30 cases in men under forty who had dissecting aneurysms of the aorta and who died during the initial attack. In these cases the elastica was much more destroyed than the muscle. Older patients may show more destruction of the muscle layer. Gore also noted that the dissecting aneurysms were often associated with congenital anomalies. In this case there was no innominate artery.

DR. LINTON: In this case, were there other congenital anomalies?

DR. CASTLEMAN: We found nothing that would suggest a Marfan syndrome, although that is often associated with a dissecting aneurysm.

DR. ALFRED KRANES: Is it not unusual to see medial necrosis in a young person with a normal blood pressure?

DR. CASTLEMAN: It is not characteristic of the younger patients with changes in the media of the aorta to have associated hypertension. Most of the older patients, on the other hand, have had hypertension.

DR. CURRENS: Was there involvement of the left iliac artery?

DR. CASTLEMAN: No; I do not know what the cause of the diminished pulsation in the left leg was.

DR. CURRENS: The normal size and caliber of the aorta as far as the arch demonstrable by angiogram could be used as an argument against syphilitic aortitis. The syphilitic aorta is a dilated aorta where it is involved by the disease.

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CASE 39402

PRESENTATION OF CASE

A twenty-seven-month-old girl was referred to the hospital because of abdominal pain.

Her mother said that for the past two months the patient had had episodes of abdominal pain beginning at any time of the day or night, lasting less than one minute, occurring once or twice a day and apparently being unrelated to bowel movements, meals or activity. At those times the child pointed to the middle of the abdomen, said "sore tummy," clutched herself and then in a little while went on playing. About six weeks before admission she had two episodes of vomiting. She did not have diarrhea, constipation, melena or pain on defecation. There had been no change in appetite; the stools had not been bulky or frothy. She was said to have put things in her mouth, and on one occasion her mother had found a pin in the stool. Repeated episodes of otitis media during the six months before admission had been treated with chlortetracycline.

Physical examination showed a well developed and well nourished child in no distress and was negative except for marked scarring of the ear drums. There were no palpable organs or masses in the abdomen. During the examination the patient complained of a "sore tummy" but permitted deep abdominal palpation without guarding.

The temperature, pulse and respirations were normal.

The urine was normal. Examination of the blood revealed a hemoglobin of 11.3 gm. per 100 cc. and a white-cell count of 8900, with 55 per cent neutrophils, 40 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophils. A stool specimen was brown and guaiac negative. A plain film of the abdomen showed an abnormal gas pattern in the right side of the abdomen suggesting gas in loops of small bowel. Some gas and stool was seen in the descending colon and rectum. The iliopsoas-muscle shadows and properitoneal fat lines were normal. The liver was normal in size, but the spleen appeared to be enlarged. On barium-enema examination (Fig. 1) the barium flowed readily

through the rectum and a loop of sigmoid and up the descending colon without revealing any abnormality. It then filled several redundant loops of large bowel that occupied the left side of the abdominal cavity, passed through a portion of large bowel transversely across the lower lumbar region, and appeared to pass from this portion of the colon into a narrow area of bowel through which it would not pass more than 7 cm. The last 7 cm. of bowel had the appearance of terminal ileum, and the portion of large bowel lying transversely across the lower lumbar region was thought to represent the sigmoid colon. A gastrointestinal series showed a normal-appearing esophagus, stomach, duodenum and jejunum. The ileum extended up into the right upper abdomen. The mucosal pattern of the bowel appeared a little irregular, with some pooling of barium, but this may have been due to the fact that the patient would drink only a small quantity of the barium.

FIGURE 1. *Barium-Enema Examination.*
The larger portion of the colon lies within the left side of the abdomen. The arrow points to the region of the ileocecal valve.

In the hospital the patient's condition remained unchanged. On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. RAKER*: Except for the possibility of an enlarged spleen nothing in the protocol appears to suggest a lesion outside the gastrointestinal tract; therefore, I am going to eliminate all lesions except those of the gastrointestinal tract. What are the possible causes of a gastrointestinal-tract difficulty? Obviously, one is inflammation, which I am going to exclude immediately although I cannot say that the patient did not have acute appendicitis recurring over a long period and I cannot say that she did not have an acute Meckel diverticulum. The possibility of foreign body is raised by the information about a pin in a stool. Usually, foreign bodies pass spontaneously, and they are often radio-opaque; there was no definite history of a foreign body and nothing to suggest a hairball in the stomach so that I am going to eliminate that.

Mechanical factors appear to be the most likely possibilities. A hernia had not been reported. There was no history of any previous operations so that I do not expect a band adhesion of that kind. That brings me immediately to the most likely diagnosis — namely, some congenital abnormality. There are two categories of congenital defects in the gastrointestinal tract: the first includes all causes of permanent changes in the bowel, and the second includes causes of recurring abnormalities that between episodes leave a fairly normal bowel.

Of the permanent changes, I cast out atresia because the child was much too old and atresia would have been discovered and treated much sooner than this. Did she have stenosis? We know that embryologically there is the possibility of a diaphragm-like stenotic area in the small bowel or even in the large bowel, which could contain an opening wide enough to permit a child to go on to this age with recurrent episodes of pain and give a picture something like this. In the Children's Hospital series[1] 8 of the 71 patients with stenosis were older than a year, and 1 was nine. However, these patients are usually feeding and nutritional problems and they have scanty stools containing curds. These findings were not reported in this particular child; indeed, it was clearly stated that she was well developed and well nourished. That statement argues somewhat against the possibility of a permanent abnormality in the gastrointestinal tract

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and is in favor of an intermittent obstruction. I shall cast out annular pancreas on the same basis that I cast out stenosis, for I think it is even less likely. An annular pancreas is usually higher in the gastrointestinal tract than this lesion was.

Did she have a duplication of the intestine? Of course I cannot exclude that entirely, but no mass was felt and none was suggested in the x-ray report. There was no evidence of hemorrhage as there sometimes is if the duplication has a communication with the bowel. I cannot exclude it, but I do not think it is very likely unless it was a very small duplication that caused intussusception.

What about intermittent causes of obstruction? I think I am more likely to find the correct diagnosis in this group. Intussusception is the first one that comes to mind. The child could have had a Meckel diverticulum that had intussuscepted from time to time, giving a picture just like this, or a duplication that was doing the same thing. There are some points against intussusception, however. No mass was ever described either by palpation or in the x-ray films, no melena was observed, and the guaiac test on the stool was negative. Of course those two facts do not exclude intussusception completely, but there is usually evidence of blood in the stool; about 85 per cent of the patients in most series of intussusception have some melena. I cannot exclude it entirely, but I do not think it the most likely cause of this patient's trouble.

The most likely cause in my mind is some condition producing an intermittent volvulus. The x-ray film itself suggests a malrotation of the large bowel. There are two main difficulties associated with malrotation. Usually, there is a band from the malrotated cecum that crosses the duodenum and may obstruct it at some point. This band, however, need not be present, and it does not seem to have been present here because there was no evidence of duodenal obstruction. The child did not vomit much, and the x-ray report did not describe any dilatation or deformity of the duodenum.

This child could have had the other condition that accompanies a malrotation — namely, an abnormally mobile mesentery of the cecum and perhaps small bowel, with malrotation of the cecum and volvulus of the small bowel about the mesentery itself. In the Children's Hospital series 29 of 156 patients with malrotations had symptoms just like this that lasted longer than a year before operation was performed — 1 patient was fifteen years old. The volvulus of the small bowel is usually clockwise; 1, recorded in the book by Ladd and Gross,[2] was twisted four times around itself. These malrotations may untwist, and the patient may have a fairly normal course between episodes.

Finally, there could have been multiple lesions in this case. Of these 156 patients with malrotation in the Children's Hospital reports, 118 had malrotation alone, and 28 had an additional congenital abnormality, including duplication, duodenal stenosis and others.[3]

In conclusion, before I look at the x-ray films (perhaps Dr. Hanelin will make me change my mind), I am going to say that the most likely diagnosis is an intermittent volvulus of the small bowel based on a malrotation of the intestine. The second diagnosis, which I cannot exclude but think is less likely, is intussusception, which of course could be from a Meckel diverticulum or duplication. My third choice, far down the list, is stenosis of the ileum.

I have some questions to ask you when you show me the x-ray films, Dr. Hanelin.

Dr. Joseph Hanelin: From the roentgenographic standpoint the principal abnormality consists of malrotation of the bowel, with all the colon lying on the left side (Fig. 1). The course of the large bowel is better detected in the postevacuation films. The cecum is directed toward the right, and the ileum extends upward and to the right from the ileocecal valve. There is no obstruction of the large bowel. An upper gastrointestinal examination that was done subsequently shows no abnormality of the esophagus, stomach or duodenum. There is normal progress of the barium through nondistended loops of bowel. No abnormal masses are evident in the abdomen.

Dr. Raker: You have already answered most of my questions. Since you see no evidence of a stenotic area in the small bowel, no mass and no evidence of any double flow of barium, I shall stand on my previous discussion.

Clinical Diagnoses

Volvulus.

Incomplete rotation of bowel.

Dr. John W. Raker's Diagnosis

Malrotation of large bowel, with intermittent volvulus of small bowel.

Anatomical Diagnosis

Malrotation of large bowel.

Pathological Discussion

Dr. Robert H. Fennell, Jr.: Dr. Shaw, would you describe your operative findings.

Dr. Robert S. Shaw: Our reasons for operating on this patient were those that Dr. Raker outlined. We thought she might have had a chronic volvulus of the midgut producing her nondescript crampy abdominal symptoms. She lacked the usual vomiting and distention. Her chief complaint was pain. On opening the abdomen we encountered normal-appearing small bowel. When the bowel was delivered from the peritoneal cavity, it was seen to be malrotated. The entire small bowel and the large bowel down to the descending colon were attached by means of a stem-like mesenteric base, which contained the superior mesenteric artery. There was a clockwise rotation of a little less than half a turn. I really did not think that the degree of volvulus observed at operation would have caused symptoms. As Dr. Raker expected, there was no attachment of the cecum across the duodenum. There was a marked mesenteric adenitis, with masses of matted lymph-node tissue measuring up to 3 cm. in diameter. One of the lymph nodes was removed for biopsy. Nothing further was done except for an appendectomy. The bowel was replaced in the peritoneal cavity, and the abdomen was closed. Some surgeons have recommended attempting to reattach the bowel mesentery in its normal position, but Ladd and Gross believe that if any attachments of the colon to the right side are divided and the colon allowed to slide to the left recurrence is unlikely.

Postoperatively, this patient has continued to have some episodes of crampy abdominal pain; they are less frequent, but they have been a problem to the parents. She has come back into the hospital on two occasions because of abdominal cramps. She has had repeated gastrointestinal x-ray studies, and on one film a shadow very suggestive of an ileoileal intussusception was seen. Intermittent obstruction of the ileum on this basis might explain the picture she presents. I think Dr. Raker has just as good an idea of what is going on here as we do.

Dr. Fennell: The lymph node showed nothing but hyperplasia. The appendix was perfectly normal. Do you think the rotation could have taken place periodically and at the time we found her she did not have it?

Dr. Shaw: She might have had intermittent volvulus and still may have it. Ladd and Gross[2] described cases of malrotation and volvulus in older children presenting chronic recurrent, mild symptoms or occasionally the celiac syndrome. It was thought preoperatively that the patient might fall into this group. Here the importance of dividing attachments of the right colon or cecum and allowing the colon to slip to the left is stressed. Recurrent volvulus is thought not to occur because this maneuver produces widening of the pedicle of the potential volvulus. In the case under discussion at operation there was no attachment of the ascending colon and the anatomic arrangement already allowed displacement of the entire colon to the left with complete exposure of the duodenum.

I believe that operation was justified here because of the possibility of attachments in the ascending colon that might have been advantageously divided. Obviously, little was accomplished except for clarification of the anatomic abnormality. The actual mechanism of the patient's symptoms is still not clear.

Dr. Raker: Gross[1] has recorded, in the latest edition, a patient in whom the volvulus recurred with a fatal outcome.

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EDUCATION OF NURSES

NURSING, by perseverance and self-improvement, has joined the family of professions albeit by the back door. Despite progress made, its exact position is sometimes in doubt and its ultimate status in dispute. Nursing education is the definitive resolvent. Some believe that nursing requires only preparation sufficient for the servants' quarter; others advocate fitting training to admit all members to the family board. Understanding of the evolution of the various types of nursing and of the preparatory requirements for each will do much to clarify the position of nursing as a profession.

In the past, the hospital received the bulk of its nursing staff through the inexpensive system of apprentice training. Increased technical and scientific knowledge involved in the care of the sick has necessitated differentiation of levels of nursing and broader basic education. There is need for improvement in nursing education as well as for recognizing and understanding the distinctions between the various types of nursing required for the total care of a patient.

An academic degree is not a prerequisite for all who care for a patient any more than sympathy and compassion alone are sufficient qualifications. Ever since physicians relegated temperature taking to nurses, more and more procedures have followed. In like manner, nurses (sometimes grudgingly) have given over many of their simpler duties to the auxiliary personnel of practical nurses, aides and ward helpers. From the total care of the patient and his surroundings, the nurse has had to curtail her duties to a specialized area.

Hospitals need to direct their sights toward a goal of well trained professional nurses capable of handling the demands of their work as well as supervising those less highly trained. A nucleus of truly capable nurses will not only ensure better patient care but also afford economical utilization of semi-skilled persons equipped to perform simple procedures. In the hospital the student should become skilled in technics while being inculcated with the spirit of service and devotion to her calling.

Colleges must accept responsibility for ensuring teaching of high quality in the major field of nursing. Acceptance of inadequate and superficial courses for credits in place of solid academic foundations should not be countenanced. Courses geared to the needs of nursing are a requisite. Too frequently, the degree program in nursing is not equivalent to a true collegiate program, nor is the degree conferred commensurate with its lettering.

The cost of nursing education should be considered in the same vein as the cost of other professional education. Engineers, physicians, lawyers and dietitians do not attain their professional status by being "bound out." The financial burden of educating a nurse should not be included in the hospital patient's bill any more than the academic instruction of the prospective physician should be considered as hospital operating expense.

Physicians have a definite responsibility toward improving the quality of nursing care. Their unique

position in the community affords them opportunity for wise counseling and directing of prospective candidates toward the proper level of nursing. With hospital and collegiate affiliations, physicians are in a position to assist in curriculum planning and co-ordination so that a baccalaureate in nursing will denote a standard of education and skill worthy of confidence. A physician usually sees his hospital patient but a few minutes a day; for the rest of the twenty-four hours, the patient is in the hands of a nurse, especially in hospitals without interns. It seems prudent for such a trust to be given to those qualified to assume it. Physicians, as the most highly trained profession, should not expect their assistants to bear the responsibility for interpreting their orders without sufficient knowledge and understanding. It is well to admit that when nurses do not measure up to the expectations of the medical profession the fault lies not in too much education, as frequently suggested, but rather in too little or improper education.

Those recognizing the folly of sending a boy to do a man's errand but subscribing to the folly of sending an inadequately trained girl to perform duties requiring a woman of mature and sound education will welcome the Russell Sage Foundation publication, *Collegiate Education for Nursing*, by Dr. Margaret Bridgman. With clear insight, common sense and discernment derived from first-hand study, Dr. Bridgman has stated the need for sound educational policies in the diverse and bewildering pattern of current teaching programs in nursing. She has set forth standards of preparation that will not only improve the quality of nursing care but also give nursing an indisputable place in the family of professions.

JAMES LIND ON SCURVY

THERE is nothing new under the sun. Nevertheless the probability that vitamin C has been preventing scurvy since mammalian life appeared upon the globe, and the fact that Sir Richard Hawkins appreciated the utility of fruit juice for this purpose as early as 1593 do not detract from the part that James Lind played in a scientific appraisal of this observation, by controlled experiments, just two hundred years ago.

The *British Medical Journal*, commenting in a leading article of June 6, 1953, on the appearance of Lind's "Treatise on Scurvy" in 1753 and the commemorative symposium of the Nutrition Society held this year at the University of Edinburgh, notes that his conclusions were the results of actual experimental tests carried out on HMS *Salisbury*, a "50-gun fourth-rater," at a time when losses from scurvy ran sometimes as high as 3 out of 4 seamen.

Nor was this the only contribution of the Scot who may well be regarded, according to the *British Medical Journal*, "as the true founder of the Royal Naval Medical Service." He established rules for the prevention of typhus on shipboard; he devised a method of distilling sea water; he published in 1757 his famous treatise "On the Most Effectual Means of Preserving the Health of Seamen," and in 1768 an "Essay on Diseases of Europeans in Hot Climates" appeared.

Through Lind, a graduate in medicine of the University of Edinburgh, the British Navy may be said to have benefited from the teachings of the great Boerhaave as the British Army did through Sir John Pringle. For as the Scottish Pringle had been a pupil of Boerhaave at Leyden, so Lind, a generation removed, was a pupil of a pupil of the Dutch master.

WHERE LEAD THE PATHS OF GLORY

FORTUNATELY for most men, as Sir William Osler aptly expressed it, "we go out of life as we came into it, unknowing and unafraid." And yet a realization that the end is definitely approaching, although still perhaps days, weeks or months away, is an experience to which many must adjust. It is in such a situation that soundness of basic philosophy of life, strength of character and religious principles are called into play. Often toxic factors or organic cerebral damage so alters the picture that normal intellectual activity is modified and, as he faces the final call, a person is definitely "not himself." And yet there are some in whom no amount of physical suffering, of toxemia or of drugs can produce a change in their basic reactions to their fellow human beings, nor can the specter of death in their path unnerve them. Every practitioner of long experience has met such persons and has derived

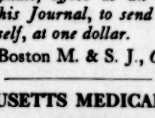
inspiration and support from his experience in dealing with them. In the medical profession such names as Francis Peabody, Elliott Cutler, Hans Zinsser and many others come to mind.

And out of these considerations arises another question, which every practicing physician must face repeatedly and which always requires an answer: Shall he or shall he not tell the patient who is fatally ill that he is going to die? This is a much-discussed question to which there is no categorical answer. The doctor must make a special and, hopefully, an appropriate decision in every case. Probably the demoralized and apprehensive person, desperately clinging to a hope of life, should usually be allowed to delude himself. And yet it appears to be the experience of most physicians that the majority of patients who have been fairly sound and well adjusted throughout their lives accept the fact of impending death with calmness and often with apparent relief. When all uncertainty is cleared away, and all suspicion of deception and camouflage on the part of the doctor and the family are removed, it seems to be the rule that the patient appears relatively content with the verdict and asks only for as much relief of suffering as can be accorded to him. And in the eyes of the attending physician, as he sees his patient thus courageously approach the abyss, there is a certain glory, a certain inspiring grandeur that he will not forget.

Dr. Curtis, editor of the Physico-medical Recorder, Cincinnati, offers as an inducement to subscribe for his Journal, to send a lithographic profile of himself, at one dollar.

Boston M. & S. J., *October 5, 1853*

MASSACHUSETTS MEDICAL SOCIETY



JOHN MATHEWS BIRNIE
1878–1953

Dr. John M. Birnie died on August 8, 1953, in Springfield. Except for the years at Williams College, at Harvard Medical School and at the German Hospital of Philadelphia, where he served his internship under Dr. John Deaver, he lived out his days in his native city. Recognized as a well trained surgeon, he rose to top posts on the staffs not only of Springfield hospitals but also of many in the Connecticut Valley.

Dr. Birnie always took great interest in the non-professional affairs of medical practice. For this interest he was rewarded with appointment for a seven-year term on the Massachusetts Board of Registration in Medicine, and with election to positions of honor in the many societies to which he belonged, among which was the presidency of the Massachusetts Medical Society. He will be remembered as the president who started the move for a permanent home for the society and thereafter furthered the project diligently. Just is it indeed that he lived to see his dream come true.

Not the least of his attributes was his sociability. He had a tenor voice, trained while on the Williams College Glee Club, and a repertoire of songs that enlivened the lighter moments of medical meetings. He was an ardent Rotarian and had served a term as president of the local club. His hobby was antique furniture, about which he could talk with authority. His home harbored many an old chair, table and chest that he had collected, restored when necessary, and fondly preserved. In spite of his many interests, professional and otherwise, Dr. Birnie was a home-loving man, devoted to his family and zealous for its welfare. His death leaves a void in his community and in his profession second only to that in his household.

DEATHS

ROCHFORD — Richard A. Rochford, M.D., of Springfield, died on September 10. He was in his sixty-fifth year.

Dr. Rochford received his degree from Harvard Medical School in 1914. He was senior surgeon, Mercy Hospital, Springfield, and formerly was a member of the Springfield Board of Health. He was a fellow of the American College of Surgeons and the American Medical Association.

He is survived by his widow, two sons, four daughters and a grandson.

SIDELL — Samuel Sidell, M.D., of Brookline, died on September 12. He was in his fifty-second year.

Dr. Sidell received his degree from Tufts College Medical School in 1926. He was a member of the staffs of the Beth Israel, Boston City, Whidden Memorial, Chelsea Memorial, Cambridge City and Booth hospitals and the New England Hospital for Women and Children. He was a member of the New England Obstetrical and Gynecological Society and the Greater Boston Medical Society.

He is survived by his widow, a son, his mother and three brothers.

WHELAN — Edmond V. Whelan, M.D., of Springfield, died on September 13. He was in his sixty-eighth year.

Dr. Whelan received his degree from Tufts College Medical School in 1909. He was formerly vice-president of the staff of the Mercy Hospital and school physician in Springfield.

He is survived by his widow, five brothers, two sisters and several nieces and nephews.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Differentialdiagnose innerer Krankheiten: Eine kurzgefasste Darstellung für Ärzte und Studierende. By Dr. Robert Hegglin, lecturer, Universität Zürich. Second revised edition. 8°, cloth, 556 pp., with 250 illustrations. Stuttgart: Georg Thieme, 1953. DM 55.- (Distributed by Grune and Stratton, New York.)

The first edition of this book on the differential diagnosis of internal diseases was published in 1952 and soon went out of print, an indication of its popularity. The author has revised this new edition and added chapters on headache and pain in the extremities. There is an extensive index, and the publishing is excellent.

Conduction Anesthesia. By George P. Pitkin, M.D. Edited by James L. Southworth, M.D., Robert A. Hingson, M.D., F.I.C.A., F.I.C.S., F.(Faculty of Anes.) R.C.S. (England), first director anesthesia, Women's Division (Philadelphia Lying-in Hospital), of Pennsylvania Hospital, and first professor of anesthesia, University of Tennessee School of Medicine; and Winifred M. Pitkin, M.A. (Oxon.), B.M., B.Ch. (Oxon.), M.R.C.S. (Eng.), L.R.C.P. (Lond.), M.D. Second edition. 4°, cloth, 1005 pp., with 585 illustrations. Philadelphia: J. B. Lippincott Company, 1953. $22.50.

The first edition of this standard work was published in 1946. This second edition has been revised and brought up to date by a group of 3 editors. Chapters and material have been added on the vertebral canal and its contents, topical anesthesia for the ophthalmologist, the oral and general surgeon, and the complications of conduction anesthesia and their prevention. The sections on pharmacology have been revised. There is a bibliography of 14 pages and indexes of authors and subjects. The book should be in all medical libraries and in the collections of anesthesiologists.

Transactions of the American Goiter Association. 1952 Annual Session, May 1, 2 and 3, Chase Hotel, St. Louis, Missouri. 8°, cloth, 429 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1953. $12.50.

This annual volume of an important serial contains a large number of papers on various aspects of goiter and the thyroid gland, as well as the Van Meter prize essay on radioactive thyrotropic hormone preparations. Future volumes could be much improved by indexes. The complete series should be in all medical libraries and in all collections on the subject.

Die Geburtshilflichen Operationen: Ihre Ausführung und Anwendung. Ein Lehrbuch für Studierende und Gebrauchsbuch für Ärzte. By Prof. Dr. Med. Heinrich Martius, director, Universitäts-Frauenklinik, Göttingen. Seventh revised edition. 8°, cloth, 290 pp., with 268 illustrations. Stuttgart: Georg Thieme, 1953. DM 34.- (Distributed by Grune and Stratton, New York.)

The first edition of this textbook on operative obstetrics was published in 1933, and the author, an eminent German obstetrician and gynecologist, has revised and brought up to date this seventh edition. Dr. Martius is the author of three other books on obstetrics and gynecology. There is a good index, and the book is well published.

The Epidemiology of Health: A New York Academy of Medicine book. Iago Galdston, M.D., editor. 8°, cloth, 197 pp. New York: Health Education Council, 1953. $4.00.

This composite book by 13 physicians is based on the eleventh annual Eastern States Health Education Conference. The subject is covered in general, and there are chapters on tuberculosis, mental hygiene, nutrition and old age in relation to epidemiology. There is a bibliography of 12 pages and a good index. The book should be in all collections on public health.

Epidemics in Colonial America. By John Duffy. 8°, cloth, 274 pp. Baton Rouge: Louisiana State University Press, 1953. $4.50.

Mr. Duffy has made an exhaustive study of the epidemic diseases that afflicted the people in America during Colonial times. There are chapters on smallpox, diphtheria and scarlet fever, yellow fever, measles, whooping cough and mumps, respiratory diseases and "agues, fluxes, and poxes." Many references are carried as footnotes to the pages; there are a bibliography of 17 pages and a good index. The printing is done with a good type on nonglare paper. The book is recommended for all history collections, general and medical.

Annual Review of Medicine. Vol. 4. Windsor C. Cutting, editor, Stanford University School of Medicine, and Henry W. Newman, associate editor, Stanford University School of Medicine. 8°, cloth, 452 pp. Stanford, California: Annual Reviews, Incorporated, 1953. $6.00.

This new volume in a standard series follows the same general pattern as the previous volumes. There are 19 articles by 23 authors on various aspects of medicine. There are indexes of authors and subjects. The series should be in all medical libraries.

Transactions of the American College of Cardiology. Vol. II, 1952. Edited by Bruno Kisch, M.D. 8°, paper, 252 pp. New York: American College of Cardiology, 1953.

This new society was organized in 1951, at a meeting in New York at which a number of papers were read and published in 1952. The transactions of the first annual meeting for 1952 have now been published. This new serial should be in all medical libraries and in the collections of cardiologists.

Die Lungenresektionen. By Prof. Dr. A. Lezius, professor of surgery, Universität Hamburg, and director Chirurgischen Universitätsklinik und Poliklinik, Hamburg-Eppendorf. With an introduction by Prof. Dr. R. Nissen, director, Chirurgischen Universitätsklinik Basel. 8°, cloth, 143 pp., with 149 illustrations. Stuttgart: Georg Thieme, 1953. DM 49.80. (Distributed by Grune and Stratton, New York.)

This semi-atlas on resection of the lung is comprehensive in its limited scope. The text is divided into general and special parts. The general part is devoted to history, indications, preoperative studies and treatment, anesthesia and methods of operation. The special part discusses in detail pneumonectomy, lobectomy, segment resection, atypical resection and postoperative treatment. It is a practical book without any references to the literature. The illustrative work and the publishing in general are excellent. It is a beautiful production and should be in all collections on the lung.

How to Improve Your Sight: Simple daily drills in relaxation. By Margaret D. Corbett, authorized instructor of the Bates Method. Revised edition. 12°, cloth, 93 pp., with illustrations. New York: Crown Publishers, Incorporated, 1953. $1.50.

This small book, first published in 1938, has gone through twelve printings to date. The text describes the William H. Bates method of rejuvenation of eyesight.

Human Factors in Air Transportation: Occupational health and safety. By Ross A. McFarland, associate professor of industrial hygiene, Harvard School of Public Health. 8°, cloth, 829 pp., with illustrations. New York: McGraw-Hill Book Company, Incorporated, 1953. $13.00.

This new work on aviation medicine and allied matters is comprehensive in scope. The material is divided into eight categories. The subjects covered comprise the nature and extent of airline operations, selection training, maintenance of health and efficiency of flight and ground personnel, safety on the ground and in flight, sanitation and health in airline operations, passenger and service problems, and health and medical services in air transportation. Bibliographies are appended to the 17 chapters. There is an extensive index, and the publishing is excellent. The book is recommended for all medical libraries and for physicians interested in aviation and its problems.

Symptoms and Signs in Clinical Medicine. An introduction to medical diagnosis. By E. Noble Chamberlain, M.D., M.Sc., F.R.C.P., senior lecturer in medicine, University of Liverpool, senior physician, Royal Southern Hospital, Liverpool, and physician-in-charge, Medical Unit, Sefton General Hospital, Liverpool. Fifth edition. 8°, cloth, 480 pp., with 354 illustrations. Baltimore: Williams and Wilkins, 1952. $8.00.

This manual was first published in 1936 and has gone through ten printings and four editions before this new edition, in which each chapter has been considerably revised, and some illustrations added. A glossary of medical terms concludes the text, and there is a good index. The printing was done in Great Britain.

Thirteenth Semiannual Report of the Atomic Energy Commission. 8°, paper, 210 pp., with illustrations. Washington, D. C.: Government Printing Office, 1953.

The material in this report is arranged in three parts: major activities in atomic-energy programs, July–December, 1952, including a section on biology and medicine; financial; and public safety in continental weapons tests.

Modern Treatment: A guide for general practice by fifty-three authors. Edited by Austin Smith, M.D., editor, *Journal of the American Medical Association;* and Paul L. Wermer, M.D., secretary, Committee on Research, American Medical Association. 4°, cloth, 1146 pp., with 13 illustrations and 65 tables. New York: Paul B. Hoeber, Incorporated, 1953. $20.00.

This composite work, written by a large number of specialists, is designed to provide the general practitioner with a useful guide to clinical problems in therapy. The material is arranged systematically, covering the field of internal medicine and the specialties. An appendix provides a table of normal clinical laboratory values. There is a comprehensive index, and the publishing is good. The book should prove useful as a handy office reference work.

B-Vitamins for Blood Formation. By Thomas H. Jukes, Ph.D., Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York. 8°, cloth, 113 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $4.00. (Publication No. 146, *American Lecture Series.*)

Dr. Jukes, in this small monograph, discusses the components of the vitamin B complex and their relation to the megaloblastic anemias of pregnancy and infancy. There are special chapters on pteroylglutamic acid and the vitamin B_{12} group of compounds. Extensive bibliographies are appended to the chapters, and there is a good index.

BCG Vaccination: Studies by the WHO Tuberculosis Research Office, Copenhagen. Report prepared under the direction of Lydia B. Edwards, M.D., chief of Field Studies, and Carroll E. Palmer, M.D., Ph.D., director. With the assistance of Knut Magnus, cand. act., assistant statistician, Tuberculosis Research Office, World Health Organization, Copenhagen. 8°, paper, 307 pp., with 50 illustrations and 85 tables. Geneva: World Health Organization, 1953. $3.00. (*World Health Organization Monograph Series.*)

This monograph is concerned with the results of an intensive study of BCG vaccination in school children. More than 40,000 children in Denmark, Mexico, Egypt and India, most of them seven to fourteen years of age, were given prevaccination tuberculin tests, on the basis of which 23,000 were vaccinated. The work has yielded important information about tuberculin allergy in children before vaccination and the allergy induced by BCG. Voluminous tables of supporting data are appended to the text. The monograph should be in all collections on tuberculosis and medical sociology.

Plastic Surgery at The New York Hospital One Hundred Years Ago, with Biographical Notes on Gurdon Buck. By Herbert Conway, M. D., and Richard B. Stark, M.D. 8°, cloth, 110 pp., with 29 illustrations. New York: Paul B. Hoeber, Incorporated, 1953. $5.00.

The New York Hospital-Cornell Medical Center of today began in 1771 as the Society of the New York Hospital, when a charter was granted by King George III of England. Dr. Gurdon Buck joined the hospital as attending surgeon in 1837 and was active for forty years. He was a pioneer in plastic surgery, and his well known book, *Contributions to Reparative Surgery*, a classic in its field, was published in New York in 1876. The present book, which furnishes a joint account of the hospital and of Dr. Buck's work, should be in all collections on medical history and surgery.

Your Arthritis: What You Can Do About It. By Alfred E. Phelps, M.D. Revised edition. 12°, cloth, 192 pp., with 10 illustrations by James MacDonald. New York: William Morrow and Company, 1953. $3.00.

This small book for the laity was first written in 1943. The author has revised the text and brought it up to date. The role of cortisone, hydrocortisone and ACTH is discussed, and the results of their use evaluated. There is a special chapter on the work of the Arthritis and Rheumatism Foundation, established in 1947, under the sponsorship of the American Rheumatism Association. The publishing is good.

Office Orthopedics. By Lewis Cozen, M.D., attending physician, orthopedic staff, Orthopedic Hospital, Veterans Administration Hospital, Los Angeles County Hospital, Cedars of Lebanon Hospital, Los Angeles, and Los Angeles Tuberculosis Sanitarium, Monrovia, California, and assistant professor of orthopedic surgery, College of Medical Evangelists, Los Angeles. Second edition. 8°, cloth, 304 pp., with 191 illustrations. Philadelphia: Lea and Febiger, 1953. $5.50.

In this new edition Dr. Cozen has reviewed the whole text of his book and added material and illustrations. The uses of new drugs that are meeting with apparent success are described. The references have been brought up to date. There is a good index, and the publishing is excellent.

John Abernethy: A biography. By John L. Thornton, A.L.A., librarian, St. Bartholomew's Hospital Medical College. 8°, cloth, 184 pp., with 8 illustrations. London: Simpkin Marshall, Limited, 1953. 25/-net.

This new biography of an eminent British physician of the eighteenth century, written by a well known London librarian, is based on all the existing documentary evidence, is meticulous in detail and is written without prejudice. There is a bibliography, as well as a chronologic list of the writings of Abernethy. The small book should be in all collections on biography, medical and general.

Syphilitic Optic Atrophy. By Walter L. Breutsch, M.D., clinical professor of neurology and psychiatry, Indiana University School of Medicine, clinical director and head of the research department, Central State Hospital, Indianapolis, and special consultant to the United States Public Health Service, Division of Venereal Diseases, Washington, D. C. 8°, cloth, 138 pp., with 27 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $5.50. (Publication No. 142, *American Lecture Series.*)

Dr. Breutsch emphasizes the importance of early diagnosis and treatment to prevent blindness, discussing the pathogenesis of the disease based on microscopical study of the visual pathways of 80 patients with all types of syphilis of the central nervous system. There is a bibliography of 127 references. The monograph should prove of value to ophthalmologists and neurologists.

Ocular Therapeutics. By William J. Harrison, M.D., Phar. D., attending surgeon, Wills Eye Hospital, consulting ophthalmologist, Pennsylvania Railroad, and associate professor in ophthalmology, Jefferson Medical College, Philadelphia. Second edition. 16°, cloth, 282 pp. Springfield, Illinois: Charles C Thomas, 1953. $6.50.

This new edition has been revised to include the official drugs in the *United States Pharmacopoeia XIV*, *National Formulary IX* and the 1950 edition of *New and Nonofficial Remedies.* Chapters on anticoagulants, and the ophthalmic uses of the therapeutic hormones, cortisone and ACTH have been added. Much new material has been incorporated, and a number of the chapters have been rewritten and enlarged. There is a good index; the book is issued in pocket size.

Kinderärztliche Notfallfibel: Abwehr akuter Lebensbedrohung. By Prof. Dr. B. DeRudder, director, Univ.-Kinderklinik, Frankfurt (am Main). Second edition. 8°, cloth, 164 pp., with 11 illustrations. Stuttgart: Georg Thieme, 1953. DM 13.50. (Distributed by Grune and Stratton, New York.)

The first edition of this monograph on acute emergencies in children was published in 1949. The author has revised and brought the book up to date. There is a good index, and the publishing is excellent. The small book should prove of value to German-reading pediatricians.

Hypersplenism: A clinical evaluation. By Cyrus C. Sturgis, M.D., chairman, Department of Internal Medicine, Professor of internal medicine and director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan Medical School. 8°, paper, 97 pp., with 5 illustrations and 8 tables. Springfield, Illinois: Charles C Thomas, 1953. $3.25. (The Beaumont Lecture, Wayne County Medical Society, January 21, 1952; Publication No. 175, *American Lecture Series.*)

Dr. Sturgis discusses the various aspects of hypersplenism, an entity due to an abnormal activity of the spleen. There is a bibliography of 81 references and a good index.

Physiological and Therapeutic Effects of Corticotropin (ACTH) and Cortisone. By Dwight J. Ingle, M.S., Ph.D., senior research scientist (physiologist), Research Laboratories, Upjohn Company, Kalamazoo, Michigan; and Burton L. Baker, M.S., Ph.D., professor of anatomy, University of Michigan Medical School. 8°, paper, 172 pp., with 6 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $5.50. (Publication No. 179, *American Lecture Series.*)

Dr. Ingle, in this monograph, discusses and evaluates the literature on ACTH and cortisone on the basis of 324 articles, dating from 1916 to 1951.

Stedman's Medical Dictionary. Edited by Norman B. Taylor, V.D.. M.D.. F.R.S.C., F.R.C.S. (Edin.), F.R.C.P. (Can.), M.R.C.S. (Lond.), University of Western Ontario. With the collaboration of Lieutenant Colonel Allen E. Taylor, D.S.O., M.A., classical editor. Eighteenth revised edition, with etymologic and orthographic rules. 8°, cloth, 1561 pp. Baltimore: William and Wilkins, 1953. $11.50.

This new edition of a standard dictionary has been revised and brought up to date. Several thousand words and nearly 600 illustrations have been added. Trade names have been excluded, and anatomic names previously given in Latin have been translated into English and placed in their proper place in the alphabetic arrangement in the form of tables. The publishing is excellent.

Hypnosis in Modern Medicine. Edited by Jerome M. Schneck, M.D., clinical associate in psychiatry, College of Medicine, State University of New York, and psychiatric consultant, Westchester County Department of Health. 8°, cloth, 323 pp. Springfield, Illinois: Charles C Thomas, 1953. $7.50.

This composite book written by 11 American and British specialists considers the use of hypnosis in internal medicine, surgery, anesthesiology, dermatology, obstetrics and gynecology, psychiatry (including child psychiatry) and dentistry. The last chapter deals with the physiologic aspects. The text begins with a good history of the subject. Lists of references are appended to the chapters, and there is an extensive index. The book should be in all medical libraries.

Blood Cells and Plasma Proteins: Their state in nature. Edited by James L. Tullis. 8°, cloth, 436 pp., with illustrations. New York: Academic Press, Incorporated, 1953. $8.50.

In this volume, which constitutes No. 2 of the *Memoirs of the University Laboratory of Physical Chemistry Related to Medicine and Public Health, Harvard University*, 29 physicians and scientists contributed articles on various aspects of the subject. The material is divided into seven sections: the formed and the fluid parts of the blood; factors concerned with blood coagulation; components of human blood concerned with immunity; erythrocytes; leukocytes; enzymes of plasma; and the lipoproteins of human plasma. There are indexes of authors and subjects. The book should be in all medical libraries.

Health Saboteurs. By Robert W. Davis, M.D. 8°, cloth, 306 pp., with 47 illustrations. New York: Pageant Press, 1953. $4.00.

Dr. Davis characterizes the tonsils as health saboteurs and advocates the practice of early tonsillectomy. He discusses their diseases and their relation to other diseases and conditions. A glossary of terms and a bibliography are appended to the text, but there is no index — a serious omission.

Doctor in the House. By Richard Gordon. 8°, cloth, 186 pp. New York: Harcourt, Brace and Company, 1953. $2.75.

Mr. Gordon, one of the younger British humorists, presents in this small book the life, loves and labors of an English medical student. Gordon, in real life, is a young London doctor.

Renal Cortical Necrosis and the Kidney of Concealed Accidental Haemorrhage. By H. L. Sheehan, D.Sc., M.D., F.R.C.P., F.R.C.O.G.; and H. C. Moore, M.D., of the department of pathology, University of Liverpool, England. 8°, cloth, 186 pp., with 64 illustrations and 8 tables. Springfield, Illinois: Charles C Thomas, 1953. $7.75. (Publication No. 167, *American Lecture Series.*)

The material in this monograph is largely based on the study of a series of cases at the Glasgow Royal Maternity Hospital during 1935 to 1945. The literature to March, 1952, has been reviewed as fully as possible. A seven-page bibliography is appended to the text, and there is a good index. The illustrative work and the publishing in general are excellent. The book should be in all collections on diseases of the kidney.

The Grassi Block Substitution Test for Measuring Organic Brain Pathology. By Joseph R. Grassi, M.A., director of clinical psychology and assistant professor of clinical pathology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina. 8°, paper, 75 pp., with 15 illustrations and 1 table. Springfield, Illinois: Charles C Thomas, 1953. $3.00. (Publication No. 149, *American Lecture Series.*)

The author discusses the technic, scoring and interpretation of his psychologic test for measuring deterioration. He presents a number of illustrative cases and discusses standardization. A list of references is appended to the text, and there is a good index.

Stress and Disease. By Harold G. Wolff, M.D., professor of medicine (neurology), Cornell University Medical College, and attending physician, New York Hospital. 8°, cloth, 199 pp., with 38 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $5.50. (Publication No. 166, *American Lecture Series.*)

This monograph considers stress or pressure and its relation to disease in man. The text is divided into three parts: the nature of stress; experimentally observed effects of stress; and the patient-physician relation and the alteration of attitudes and bodily reactions. The pertinent literature is reviewed. There is a bibliography of 210 references, as well as indexes of authors and subjects.

Physiology of Exercise. By Laurence E. Morehouse, Ph.D., associate professor of physical education, University of Southern California; and Augustus T. Miller, Jr., Ph.D., M.D., professor of physiology, University of North Carolina School of Medicine. Second edition. 8°, cloth, 355 pp., with 49 illustrations and 8 tables. St. Louis: C. V. Mosby Company, 1953. $4.75.

In this new edition a book first published in 1948 has been revised and brought up to date. Material has been added specially on fatigue, fitness and training. Lists of references are appended to the chapters, and there is a good index. The book should be in all medical libraries.

Physical Examination of the Surgical Patient. By J. Englebert Dunphy, M.D., associate clinical professor of surgery, Harvard Medical School, surgeon, Peter Bent Brigham Hospital, and consultant in surgery, Children's Medical Center; and Thomas W. Botsford, M.D., clinical associate in surgery, Harvard Medical School, senior associate in surgery, Peter Bent Brigham Hospital, and associate in surgery, Children's Medical Center. 8°, cloth, 326 pp., with 188 illustrations. Philadelphia: W. B. Saunders Company, 1953. $7.50.

NOTICES

MIDDLESEX WEST DISTRICT MEDICAL SOCIETY

A meeting of the Middlesex West District Medical Society will be held in the nurses' residence of the Milford Hospital, Milford, Massachusetts, on Wednesday, October 7, at 12 noon, in conjunction with the fiftieth-anniversary celebration at the hospital.

NATIONAL FOUNDATION FOR INFANTILE PARALYSIS POSTDOCTORAL FELLOWSHIPS

The National Foundation for Infantile Paralysis announces the availability of a limited number of additional postdoctoral fellowships to candidates whose interests are research and teaching in medicine and the related biologic and physical sciences. The purpose of these National Foundation fellowships is to increase the number of professional workers qualified to give leadership in the solution of basic and clinical research problems, including those of poliomyelitis and other crippling diseases.

The fellowships cover a period of one to five years. Stipends will range from $3600 to $7000 a year, with marital and dependency status considered in determining individual awards. Institutions that accept fellows receive additional compensation for expenses incurred in relation to their training programs.

Eligibility requirements include United States citizenship (or the declared intention of citizenship), sound health and the degree of M.D., Ph.D., or the equivalent. Selection of candidates is made by a fellowship committee composed of leaders in the fields of medical research and professional education.

Complete information may be obtained from the Division of Professional Education, The National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

AMERICAN SOCIETY FOR THE STUDY OF STERILITY AWARD

The American Society for the Study of Sterility announces the opening of the 1954 contest for the outstanding contribution to the subject of infertility and sterility. The winner will receive a cash award of $1000, and the essay will appear on the program of the 1954 meeting of the Society. Essays must be submitted before March 1, 1954. Further information may be obtained from the Secretary, Dr. Herbert H. Thomas, American Society for the Study of Sterility, 920 South 19th Street, Birmingham, Alabama.

SOCIETY MEETINGS AND CONFERENCES

October 4–9. American Academy of Pediatrics. Page 1126, issue of June 25.
October 5, 7 and 9. Edward K. Dunham Lectures. Page 546, issue of September 24.
October 5–December 7. Postgraduate Seminar in Neurology and Psychiatry. Page 428, issue of September 3.
October 5–December 21. Hartford Medical Society Program. Page 260, issue of August 6.
October 7. Middlesex West District Medical Society. Notice above.
October 7–December 2. Course in child psychiatry (pediatric neuropsychiatry). Page 428, issue of September 3.
October 8. New York Diabetic Association. Page 470, issue of September 10.
October 12–14. National Gastroenterological Association. Page 260, issue of August 6.
October 12–14. Medical and Dental Military Symposium. Page 470, issue of September 10.
October 12–17. Seventh International Congress of Pediatrics. Page 170, issue of July 23.
October 13. New York Society for Circulatory Diseases. Page 506, issue of September 17.
October 14. New England Cardiovascular Society. Page 546, issue of September 24.
October 15 and 16. New England Tuberculosis Conference. Hotel Bradford, Boston.
October 15–17. Annual Course in Postgraduate Gastroenterology. Page 260, issue of August 6.
October 16. New England Society of Anesthesiologists. Page 428, issue of September 3.
October 17–20. American Association of Blood Banks. Page 1126, issue of June 25.
October 19–30. New York Academy of Medicine. Page xvii, issue of June 11.
October 21–23. International Symposium on Virus Infections. Page 546, issue of September 24.
October 23 and 24. Eastern Section of American Trudeau Society. Page 506, issue of September 17.
October 25–29. American Institute of Dental Medicine. Page 124, issue of July 16.
October 28. New England Obstetrical and Gynecological Society.
November 2–4. New England Postgraduate Assembly. Hotel Statler, Boston.
November 6 and 7. American College of Cardiology. Page 506, issue of September 17.
November 12–14. Annual Convention of the National Society for Crippled Children and Adults. Chicago.
November 18. Massachusetts Society of Examining Physicians. Page 546, issue of September 24.
November 19 and 20. Inter-Society Cytology Council. Page 170, issue of July 23.
December 6. American Academy of Dental Medicine. Page 170, issue of July 23.
May 31–June 3. 1954. American Urological Association. Page xvii, issue of July 23.
September 12–15, 1954. Second International Congress of Cardiology. Page 44, issue of July 2.
September 16–18, 1954. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

District Medical Societies

MIDDLESEX EAST

November 18.
January 20. (Combined with the Auxiliary.)
March 24.
May 12. Annual Meeting. (Harlow Dinner.)

MIDDLESEX WEST

October 7. Nurses' Residence, Milford Hospital, Milford.

Calendar of Boston District for the Week Beginning Thursday, October 8

Thursday, October 8

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
4:00 p.m. Combined Seminar: Cancer Research Institute. Dr. Robert Collin. X-ray Diffraction and Its Application to Biological Problems. Joslin Auditorium. New England Deaconess Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Amphitheater, New England Deaconess Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

Friday, October 9

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott P. Joslin. New England Deaconess Hospital.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washington Square Health Unit, 41 Waltham Street.
5:00 p.m. Edward K. Dunham Lecture. Building D, Harvard Medical School.

Saturday, October 10

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

Monday, October 12

*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.
7:00–9:00 p.m. Combined Anesthesia Resident Training Program. Jimmy Fund Auditorium, Children's Medical Center, 35 Binney Street.

Tuesday, October 13

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Private Dining Room, New England Deaconess Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

Wednesday, October 14

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 35 Binney Street.

(*Notices concluded on page xvii*)